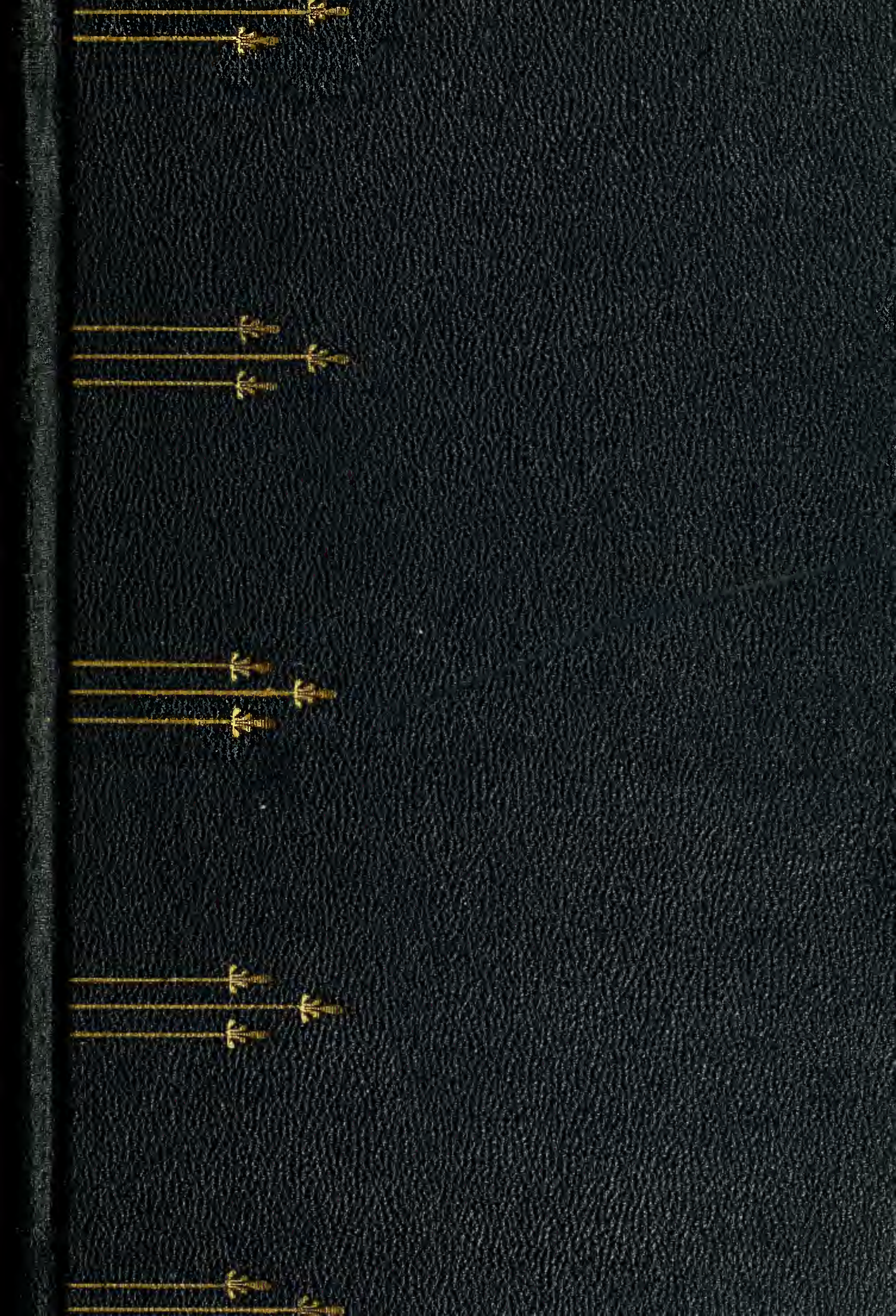

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COLLECTED PAPERS--SOUTHARD
INDEX--VOLUME I

icle
Note upon Erythragglutinins in a Cyst Fluid.
W.R.Brinckeroff & E.E.Southard
J.of Medical Research,Vol.IX,No.1,pp.28-32,Feb.1903

....

Neuropathology.
1904 E.E.Southard

....

A Case of Glioma in the Sella Turcica.
F.H.Howard & E.E.Southard.
Amer.Jour.Med.Science,Oct.1904.

....

A Case of Glioma of the Pineal Region.
1905 E.E.Southard

....

A Case of Cholesterin Stones in the Brain and Cord.
E.E.Southard
Jour.of Amer.Med.Assoc.Dec.2,1905

....

Cystic Aplasia of the Cerebral Hemispheres in an Idiot Child.
W.N.Bullard & E.E.Southard
Jour.of Med.Research,Vol.IX,No.2,pp.431-438,Jan.1906.

....

II Diffuse Gliosis of the Cerebral White Matter in a Child.
W.N.Bullard & E.E.Southard
Jour.Nerv.& Mental Disease,Jan.1906

....

II Cerebral Seizures with Suboccipital Pain: Miliary Cerebral and Gross Vertebral Aneurysms.
W.D.Ruston & E.E.Southard
Boston Med.& Surg.Jour.No.12,pp.312-314,Mar.22,1906

....

A Study of Acute Leptomeningitis.(Streptococcus Pyogenes)
E.E.Southard & R.R.Stratton
Jour.Amer.Med.Assoc.Vol.XLVII,pp.1271-1277,Oct.20,1906

....

Lesions of the Granule Layer of the Human Cerebellum.
E.E.Southard
Jour.Med.Research,Vol.XI,No.1,pp.99-116,Mar.1907.

....

Note on Cell-Findings in soft Brains.
E.E.Southard & M.B.Hodskins
Amer.Jour.of Insanity,Vol.LXIV,No.2,Oct.1907.

....

I Gliotic Cyst of the Right Superior Parietal Lobule.
A.N.Collins & E.E.Southard
Amer.Jour.of Insanity,Vol.LXIV,No.2,Oct.1907.

....

II Diffuse and Focal Lesions in a Case of late Epilepsy.
E.E.Southard
1908

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VOLUME I - (2)

XIV A Complicated Case of Brain Tumor.
C.Ricksher & E.E.Southard
Amer.Jour.of Insanity,Vol.LXIV,No.4,Apr.1908

....

XV Melancholia with Delusions of Negation: Three Cases with Autopsy.
H.W.Mitchell & E.E.Southard
Jour.Nerv.& Mental Dis.May,1908

....

XVI Further Studies in Anaphylaxis.
F.P.Gay & E.E.Southard
Jour.Med.Research,Vol.XIII,No.3,June,1908

....

XVII Typhoid Menigitis: Cultivation of Bacillus Typhosus from Meninges and Mesenteric Lymph Node in a Case of General Paresis, with Note on Experimental Typhoid Meningitis in the Guinea-Pig.
E.E.Southard & E.T.F.Richards
Jour.Med.Research,Vol.XIV,No.4,pp.513-531,Dec.1908

....

XVIII Dementia Praecox,Paranoid,Associated with Bronchiectatic Lung Disease and Terminated by Brain Abscesses. (Micrococcus Catarrhalis)
E.E.Southard & J.B.Ayer
Boston Med.& Surg.Jour. Vol.CLIX,No.27,pp.890-895,Dec.190

....

XIX Observations on a Case of Protracted Cerebrospinal Syphil with Striking Intermittency of Symptoms: Attempt at Corre tion with Ascending Meningomyelitis,Cranial Neuritis, Sub cortical Encephalitis, and Focal Encephalomalacia found a Autopsy.
J.J.Putnam-E.E.Southard & A.H.Ruggles.
Jour.Nerv.& Mental Dis.Vol.37,1909

....

XX Neurophysiological Effects of Anaphylactic Intoxication.
F.P.Gay-E.E.Southard & J.G.Fitzgerald
Apr.7,1909

....

XXI Acute Encephalitis and Brain Abscess.
E.E.Southard
1910

....

XXII A Study of Errors in the Diagnosis of General Paresis.
E.E.Southard
Jour.Nerv.& Mental Dis.,Vol.37,No.1,Jan.1910

....

XXIII Anatomical Findings in Senile Dementia: A Diagnostic Stud Bearing Especially on the Group of Cerebral Atrophies.
E.E.Southard
Amer.Jour.of Insanity,Vol.LXVI,No.4,Apr.1910

XXIV Discussion of Psychic and Somatic Factors in a Case of Acute Delirium dying of Septicemia; Note Upon Experimental Guinea-Pig Infection with Staphylococcus Albus.
E.E.Southard & J.G.Fitzgerald
Boston Med.& Surg.Jour.Vol.CLXII,No.14,pp.452-458, Apr.7,1910

....

XXV A Study of the Dementia Praecox Group in the Light of certain Cases showing Anomalies or Scleroses in Particular Brain Regions.
E.E.Southard
Amer.Jour.of Insanity,Vol.LXVII,No.1,July,1910

....

XXVI Report on the Mentality of a Subject Fasting at the Nutrition Laboratory of the Carnegie Institution of Washington,Boston,Mass,from Apr.14,to May 12,1912.
1912 E.E.Southard

....

XXVII The Significance of a Homeopathic Foundation for Clinical Research and Preventive Medicine.
E.E.Southard
Boston Med.& Surgical Jour.Vol.CLXVI,No.16,Apr.1912

....

XXVIII Psychopathology and Neuropathology: The Problems of Teaching and Research Contrasted.
E.E.Southard
Jour.Amer.Med.Assoc. Vol.LVIII,pp.914-936,Mar.1912

....

XXIX Medical Contributions of the State Board of Insanity of Massachusetts: Introductory Note.
E.E.Southard
Boston Med.& Surgical Jour.Vol.CLXIX,No.15,Oct.1913

....

XXX A Series of Normal Looking Brains in Psychopathic Subjects.
E.E.Southard
Amer.Jour.of Insanity,Vol.LXIX,No.4,Apr.1913

....

XXXI Clinical and Anatomical Analysis of 25 Cases of Mental Disease arising in the Fifth Decade, with remarks on the Melancholia Question and Further Observations on the Distribution of Cortical Pigments.
E.E.Southard-&-E.D.Bond
Pro.Amer.Medico.Psycho.Assoc.June,1913

....

XXXII How Far is the Environment Responsible for Delusions?
E.E.Southard & A.W.Stearns
Jour.Abnor.Psychology,June,1913

....

XXXIII Contributions to the Neurology of the Child. I.
W.P.Lucas & E.E.Southard
Boston Med.& Surg.Jour.Sept.1913

....

XXXIV Clinical and Anatomical Analysis of Eleven Cases of Mental Disease Arising in the Second Decade, with Special Reference to a Certain Type of Cortical Hyperpigmentation in Manic-Depressive Insanity.
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Proc.Amer.Medico-Psycho.Assoc.,May,1914

I

NOTE UPON ERYTHRAGGLUTININS IN A CYST FLUID

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AND

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NOTE UPON ERYTHRAGGLUTININS IN A CYST FLUID.[1]

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AND
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Bordet (1899) pointed out that theories of agglutination must take account, not alone of bacterial agglutination, but also of the agglutination of blood corpuscles and of casein-particles.

Malkoff (1900) worked upon the agglutination of red blood corpuscles and showed that the clumping substance has specific combining affinity for the element clumped, and, furthermore, in a normal serum which clumps different cells there are as many different specific agglutinins as there are species of cells clumped. Malkoff employed the corpuscles of the goat, against which he immunized guinea-pig and pigeon.

Flexner and Noguchi (1902) studied the effect of venoms upon agglutination, as well as upon lysis, and pointed out that the red corpuscles of the rabbit are highly susceptible, whereas the corpuscles of the guinea-pig, dog, sheep, swine, and ox are less susceptible in that order.

The most recent paper we have seen is that of Ford (1902). Ford chose an agglutinin occurring in normal serum (that in rabbit serum for hen's corpuscles), produced its anti-agglutinin, produced by immunization a second agglutinin of rabbit's serum for hen's corpuscles, and then a corresponding anti-agglutinin. He found that the two anti-agglutinins were interchangeable and therefore identical. He concludes that the body obtained by immunization is merely quantitatively different from the body found normally.

The following notes concern a fluid from a non-malignant

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[1] Received for publication, Dec. 19, 1902.

parovarian cyst removed at operation. The fluid was found to dissolve and to agglutinate the red blood corpuscles of the rabbit. The fluid was heated for one half hour at 54°–59° C., whereupon hemolytic power was lost.

Clumping was obtained of the washed corpuscles of the normal rabbit, of rabbit immunized to the cyst fluid, of dog, and of one man. Other human corpuscles, including those of the patient, were never agglutinated. Agglutination of the guinea-pig's corpuscles was so slow as to be valueless for experimentation.

Upon repeated intraperitoneal injections of the cyst fluid, amounting in all to fifty cubic centimeters, a rabbit was found to yield a serum having the property of delaying or inhibiting the agglutination of its own and other rabbit corpuscles.

The serum of the patient is markedly hemolytic for rabbit corpuscles. Upon inactivation by heat no agglutinative power could be demonstrated.

The fluid (Cy) was prepared by heat for agglutination work (Cy—C, where C is the complement). Saline suspension of washed corpuscles of the rabbit (wcR) was placed in the same amount in a series of test tubes. To each was added a different amount of Cy—C, *e.g.*,

wcR+(Cy—C) gtt. i
wcR+(Cy—C) gtt. ii, etc.

That series of tubes was found in which notable clumping occurred where the observed drop was taken from the hollow of the tube, *e.g.*,

NaCl+wcR+8 (briefly for [Cy—C] gtt. viii),
NaCl+wcR+16,
NaCl+wcR+32.

With this series was taken the limiting negative,

NaCl+wcR+4.

The whole series was centrifugalized. The supernatant fluids, thus,

NaCl+4,
NaCl+8—x,
NaCl+16—x,
NaCl+32—x,

were applied in the same amount to fresh wcR. These supernatant fluids proved to cause agglutination in similar ascending series. Thus, where

$8 - x = y$, then
$16 - x = y + 8$, and
$32 - x = y + 16$.

The quantities suggested can be only qualitatively confirmed, owing to the nature of the phenomenon of agglutination. Thus

$wcR + NaCl + 8 - x$

gives no reaction, or a border-line reaction, and

$wcR + NaCl + 16 - x <$
$wcR + NaCl + 32 - x$.

SUMMARY.

The foregoing may be summed up as follows:

The cyst fluid exhibits

1. Hetero-erythragglutinins for
    (*a.*) rabbit.
    (*b.*) dog.
    (*c.*) guinea-pig (delayed).
2. Iso-erythragglutinin for one man.
3. No other iso-erythragglutinins in cases examined (no auto-erythragglutinin).

The cyst fluid is capable of developing an anti-erythragglutinin.

The patient's serum, though equally hemolytic with the fluid, shows no agglutinative power.

The rabbit erythragglutinin sustains a quantitative relation to the amounts of corpuscles agglutinated.

A definition of the type of agglutinate obtained in work like the above may serve to bring out more clearly the value of the blood corpuscles in the study of agglutinins. The kind of aggregate observed may be shortly termed poikilagglutinate in contrast with the homoagglutinate or rouleau.

Slight acquaintance with the red corpuscles shows that they clump in two forms, in one of which the arrangement might be simply termed streptic, in the other staphylic. But these terms are scarcely definite enough, as further examination shows.

In the streptic type they adhere rim upon rim to form the coinrows or rouleaux. In the staphylic type they adhere by prominent angles upon surfaces of apposition which are accidental. In the rouleaux the elements preserve to a degree their biconcavity. The corpuscles may remain biconcave in the staphylic aggregates, but they may be variously crenate, vesicular, or otherwise distorted. The elements of a rouleau are alike, whereas the unlikeness in the elements of a tridimensional clump may be striking. Thus the streptic agglutinate and the clump in three dimensions might be more strictly termed, to employ the usual prefixes, homoagglutinate and poikilagglutinate.

Nevertheless, though the elements of a rouleau tend to show biconcavity, the elements of the poikilagglutinate (such as one gets in experiments like the above) may be equally normal-looking. Though the streptic agglutinate may be said to depend upon shape of elements with change of surface or change of ambient fluid, the staphylic agglutinate is formed without regard to element shape, consistently with great variety in surface character of its units, and in the absence of its usual medium.

Striking molar changes in surface, certainly involving marked molecular redistribution, are consistent with the constant and regular occurrence of poikilagglutination. But these changes are so many and so various (crenation, vesicularity, distortion, laking tendency) that they can hardly be invoked as the cause or necessary condition of the clumping.

The phenomena of corpuscular clumping thus serve to demolish in a simple manner those theories of agglutination which regard surface changes as the essence of clumping in general. That demolition had indeed been long since practically accomplished; but the blood corpuscles seem an especially fitting weapon.

The foregoing study emphasizes once more the quantitative character of those phenomena of which hemmagglutination is one representative, sets forth a certain advantage in studying the blood corpuscles to make clear the nature of agglutination, and indicates the desirability of further work upon agglutinins and similar principles of natural occurrence in pathological fluids.

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The Journal of Medical Research, February, 1903, Vol. IX., No. 1.

NEUROPATHOLOGY

II

OUTLINE

BY

E. E. SOUTHARD

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OUTLINE OF NEUROPATHOLOGY.

CONTENTS.

PAGE

I. INTRODUCTION 1

II. GROSS LESIONS OF THE NERVOUS SYSTEM . . . 2

NUMERICAL DATA 2

CHANGES IN SIZE, SHAPE, COLOR, CONSISTENCE 3

CHANGES DUE TO MALDEVELOPMENT, 7

DISORDERS OF CIRCULATION, TRAUMA, INFLAMMATION . . . 8

INTERPRETATION OF GROSS APPEARANCES 13

III. MINUTE LESIONS OF THE NERVOUS SYSTEM . . . 15

METHODS OF EXAMINATION . . 15

REACTIONS OF THE PIA MATER AND CONNECTIVE TISSUES, THE NEUROGLIA AND EPENDYMA, THE NERVE CELL AND ITS ADNEXA . . 16

CELL APPEARANCES IN MALDEVELOPMENT, DISORDERS OF THE CIRCULATION, INFLAMMATION . . . 21

REPAIR AND REGENERATION . . 24

PRIMARY DEGENERATION . . . 25

NEW GROWTHS 26

PAGE
IV. DISEASES PECULIAR TO THE NERVOUS SYSTEM . . . 27
NERVE TRACTS 27
SECONDARY DEGENERATION . . 29
REMOTE EFFECTS OF FOCAL DESTRUCTION OF NERVE TISSUE . 29
Cerebral Palsy of Children . . . 29
Cerebral Monoplegia and Cortical Epilepsy, 30
Cerebral Hemorrhage 31
Lesions of Pons and Bulb . . . 31
Transverse Lesions of Spinal Cord . . 32
Unilateral Lesions of Spinal Cord . . 33
SYSTEM DISEASES 33
Tabes Dorsalis 34
Progressive Muscular Atrophy . . . 35
Amyotrophic Lateral Sclerosis . . . 35
Acute Anterior Poliomyelitis . . . 36
Combined System Diseases 36
MULTIPLE DISSEMINATED SCLEROSIS, 37
SYRINGOMYELIA 37
GENERAL PARESIS 38
GENERAL DISTRIBUTION OF MUSCULAR PARALYSES AND ATROPHIES, 39
V. THE NEURONE THEORY . . 40

OUTLINE OF NEUROPATHOLOGY.

I. INTRODUCTION.

The lesions of the nervous system in man are reviewed herein from the side of pathological diagnosis. But few of the data concerning normal nerve tissue are presented, and these incidentally. In a separate chapter I have pursued recent writers beyond our present basis of induction into the field of the neurone theory.

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OPPENHEIM. Diseases of Nervous System, translated by Mayer. 1904.

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II. GROSS LESIONS OF THE NERVOUS SYSTEM.

I shall first discuss the inferences which may be drawn from changes in the nervous system of gross character (size, shape, color, consistence) and follow with a consideration of these changes grouped according to their origin (maldevelopment, circulatory disorders, trauma, inflammation). The pia mater is treated together with the central nervous system as its nutrient membrane.

NUMERICAL DATA.

Average weight of male adult brain	1,358 gm.
Average weight of female adult brain	1,235 gm.
Average weight of brain at birth	383 gm.
Average capacity of male cranium	1,500 cm^8.
Average capacity of female cranium	1,300 cm^8.
Specific gravity of brain substance	1.040
Specific gravity of cord substance	1.034
Specific gravity of nerve	1.034–8

Adult skulls with a capacity of less than 1,300 cm^3. are termed nannocephalic. The intermediate capacities are termed: 1,300–1,400 cm^3., emmetrocephalic; 1,500–1,699 cm^3., encephalic. The length-breadth index is the most commonly used of the cephalic indices. The length is taken between glabella and external occipital protuberance; the breadth, between the points farthest apart in a frontal plane. The formula of the length-breadth index is

$$\frac{100 \text{ x breadth}}{\text{length}}.$$

$$\text{Thus} \quad \frac{100 \text{ x } 14.6}{19} = 76.8$$

Such a length-breadth index places the skull in the mesocephalic series. Skulls with indices lower than seventy-five are dolichocephalic. The brachycephalic index is eighty or higher. Presence of the soft parts about the skull produces an index two to three units higher. The length-breadth index averages about eighty.

The cortex of man averages 2.94 millimeters, of woman 2.91 in depth. The cortex of the left hemisphere is a trifle deeper than that of the right. The occipital cortex is somewhat shallower than the rest.

ALTERATIONS IN SIZE.

An increase in size due to true hyperplasia of the normal elements is unknown. General increase of the neuroglia elements produces in the end a loss of volume by contraction. Apparent increase in size is produced by edema of the pia, by edema of the substance, by hemorrhage, by tumor, and by internal hydrocephalus. The most striking enlargements are seen in congenital internal hydrocephalus, or in any ventricular dilatation produced before union of the cranial sutures. In these cases the dilatation of the ventricles occurs at the expense of the brain substance, so that the total volume of the cerebral substance may be decreased.

Obvious reduction of size occurs, along with characteristic alterations of shape, in the maldevelopments. Senile atrophy, general paresis, epilepsy, porencephalic defect, trauma, may show marked diminution in total mass.

Considerable increase in diameter of the spinal cord is brought about by dilatation of the central canal (hydromyelia), edema, hemorrhage (hematomyelia), tumors, and by dilatation of long fusiform cavities in the substance (syringomyelia).

Notable apparent increase in size of the lower portion of the central nervous system is shown in various degrees in spina bifida. Patent reduction in diameter of the spinal cord is shown in atrophy, notably in tabes dorsalis and in long-standing combined system diseases.

ALTERATIONS IN SHAPE.

Besides the obvious changes in shape effected by trauma and the encroachment of certain external lesions (osteophytes of the calvarium, endotheliomata of the dura mater, cholesteatoma, internal hemorrhagic pachymeningitis, metastatic tumors, inflammatory lesions of skull and dura mater), the brain shows characteristic changes of shape from many internal causes. The most common of these changes is flattening of convolutions as a consequence of heightened tension in the ventricles (internal hydrocephalus) or of generally heightened tension from the presence within the cranium of any lesion or substance which largely reduces the cranial capacity (tumor, hemorrhage, inflammatory edema).

The agency which effects flattening of convolutions may also occasion the cerebellar compression-ring from pressure upon the rim of the foramen magnum.

Opposed to the flattening of the convolutions is the narrowing of the convolutions and correspondent widening of fissures seen in senile atrophy and in local atrophies of various cause. In old age the narrowing of convolutions is a part of a more general process of atrophy, and is consequently attended by internal hydrocephalus; the increase of fluid both in the ventricles and in the meshes of the pia is compensatory (hydrops ex vacuo) to fill space in the cranial box.

From hydrops ex vacuo must be distinguished the edema of the pia of inflammatory or mechanical (in some cases cardiorenal) origin. In the latter there is no great change in shape of the brain.

Besides the general changes in shape there are obvious changes due to local contained lesions. Many of these are more evident in the isolated brain; masses of hemorrhage, abscesses, infarctions, and necrotic tumors may rupture through the pia mater upon the artificial release of tension in removing the brain.

Wide variations in the contour and complication of the gyri are still normal. Cerebral hemispheres differ widely in the development of smaller fissures and annectent gyri. From these slighter deviations from the mean, it is not possible to induce anything with respect to mental or other capacities of the subject.

Well-marked asymmetries, approximations to the smooth brains of the lower animals, and undue richness of convolutions (microgyria) occur both generally and focally.

Of the changes in shape through loss or absence of parts, one of the most characteristic is porencephaly, a condition of local funnel-shaped defect, often in the central portions of a hemisphere, of which many degrees occur up to complete fenestration of the lateral ventricle. Porencephaly and kindred defects and local atrophies follow obstetrical and other injuries, with or without infectious complications, or may be the effect of thrombosis, embolism, or vascular changes, with incomplete repair.

There is a large series of characteristic alterations in shape of developmental or intra-uterine origin. The cases of agenesia of the nervous system range as a rule from the higher more inclusively to the lower mechanisms. The agenesia may consist in almost complete absence of coördinating mechanisms, seen in the monsters (acrania, anencephaly, cranioschisis, craniorachischisis).

The lesser grades of agenesia and aplasia exhibit maldevelopment of the higher (phylogenetically newer) mechanisms, so that the brains more or less approximate those of the lower orders of vertebrates.

Still more complex are the cases in which the external aspect and contour of the brain is preserved, but in which the cerebral substance is in places quite absent, or so thinly deposited that the ventricular fluid is visible through the transparent pia and ependymal lining.

In epilepsy (both in genuine chronic cases and in the Jacksonian type) are often found focal changes of shape (local microgyria or macrogyria) some of which are probably of traumatic origin (from evident involvement of overlying tissues), but others of which remain unexplained.

ALTERATIONS IN COLOR.

The coloring of the uncut brain varies obviously with the amount of contained blood and the state of its hemoglobin. It is not so much the blood in the sulcal veins which modifies the general hue as the blood in the superficial cortical vascular system. Probably the deepest diffuse hues have been observed in fatal cases of malaria. The diagnosis of intracranial congestion is, however, rarely justified on post-mortem evidence merely. Local blood-containing lesions are striking enough.

Besides differences due to blood content, the brain shows variations in grayness and opacity which are of importance in detecting chronic alterations. There must be distinguished a heightened opacity due to thickening of the superficial glia and the focal or general opacities due to changes in the pia mater. The pial opacities are as a rule focal and are most prominent as linear markings over the veins of the sulci, notably on the vertex and along the Sylvian fossæ. The pial opacities may be quite general; but in this case the general thickening which gives rise to them is obvious. An unusually extensive system of arachnoidal villi may be confused with pial thickenings. Flecks of fibrin in edema of the vertex and miliary or conglomerate tubercles are sometimes confused with the opacity due to pial thickening. The heightened opacity due to changes in the subpial glia is more general and less easy to make out with the eye alone.

Dustlike pigmentation is often noted on the ventral surface of the cervical pia mater. Delicate white calcareous plaques in the spinal pia can in appropriate cases be confused with tubercles.

The color of the cut surface shows a series of changes dependent on the content of blood. Puncta cruenta due to venous injection are to be distinguished from perivascular hemorrhages; from the latter the blood cannot be removed by squeezing. Attention to the shade of gray and the variations in translucence will often suggest a minute search for glioses which would otherwise remain unnoted. Light may be thrown in the fresh organ upon the state of the fiber systems by scrutiny of the concentric white markings of the cortex, best shown in the occipital and central regions. Focal differences in color and translucence aid in the gross diagnosis of multiple sclerosis, glioses of whatever cause, tabetic and general paretic lesions, and heterotopia. With respect to heterotopia the possibility of manipulative dislocation of the tissues must be rigidly excluded; no other tissue of the body (except perhaps the diffluent acute spleen) is more subject to artefact by handling than the spinal cord.

ALTERATIONS IN CONSISTENCE.

Palpation of the brain and cord is made as far as possible in situ. Freezing and thawing, formalin injections, delay of many hours before autopsy, and careless removal of calvarium and spines make judgments of consistence difficult. It is especially hard to estimate a diffuse or general increase or loss of consistence. Local differences are readily determined; but the amount of connective tissue framework normal to the region must be borne in mind (thus the motor convolutions are normally wider than the occipital, and the cerebellum is almost always firm on account of its closely set lobes).

Diffuse or general increase of consistence is found in senile brains, together with atrophy of convolutions and compensatory edema of pia. A general increase of consistence accompanies the flattening and heightened resiliency of convolutions found in chronic or acute internal hydrocephalus and in cases of intracranial tumors and foreign bodies. Diffuse or general loss of consistence occurs in cases of edema of the substance. The diffluent substance of the brain and cord found after a varying period post mortem should not lead to diagnosis of non-inflammatory softening. Such diffluence almost always renders neuroglia staining unsatisfactory; but the myelin sheaths retain their staining capacity longer. The brain before and long after birth is soft and watery.

Gross judgments can readily be made of focal differences in consistence. Coördinate parts of the nervous system are compared. Focal increase of consistence is readily made out, for example, in atrophied optic nerves, in the gliosis of the dorsal columns of the cord in tabes, in the multiple sclerosis of children, in some cases of epilepsy, and very markedly in many cases of general paresis. Focal reduction of consistence is found in edema of various origin.

MALDEVELOPMENT.

Gross malformations of the nervous system are largely related to defective development in the posterior median line. The neural groove may fail to form the neural canal altogether (*craniorrhachischisis*), above (*acrania*), below (*rachischisis*).

Acrania may or may not co-exist with absence of brain (*anencephalus*). The brain may be represented by a mass of the usual shape, but unduly small (*micrencephalia*). Or the brain substance may be thinly spread over dilated ventricles which may contain several liters of fluid (*congenital internal hydrocephalus*). The cranium may be in part absent, permitting the brain and its membranes or the membranes alone to herniate (*encephalocele, meningocele*).

A similar series of malformations occur in the spinal system, where through rachischisis a number of structures are permitted to herniate and form voluminous skin-covered swellings (*spina bifida*). *Hydromyelia* is a dilatation of the spinal central canal, the analogue of internal hydrocephalus above. If the cord lies in its usual place, there may take place a dilatation and thinning of its posterior wall with hernia through the defective lumbosacral arches (*syringomyelocele*). Much more commonly the intact cord is carried posteriorly across the hernial sac to be attached to the wall of the cyst, which becomes dimpled or biscuit-shaped thereby (*myelocele*). If the central canal of such a translocated cord becomes dilated, hydromyelocele (*myelocystocele*) ensues. It is plain that surgical interference may be dangerous where cord substance lies immediately beneath the skin, but that a simple meningocele or dilated and herniating arachnoid membrane may be more favorable for operation.

Dimples, sinuses containing hairs (*pilonidal sinuses*), and cysts may develop in the median line above the anus from remnants of the posterior end of the neural groove. These structures have no relation with the spinal canal, which is, as a rule, perfectly developed.

DISORDERS OF CIRCULATION.

Emboli of a diameter large enough to lodge in the circle of Willis itself may do no harm. Smaller emboli occlude the terminal arteries given off from the circle (preferably branches of the left middle cerebral artery), and produce areas of softening (necrosis and local edema) which are often palpable from without or discernible on section. Multiple fat embolism may be found following fracture of the long bones. Air embolism and tumor embolism occur.

Arteriosclerosis gives rise, by slow occlusion or by permitting thrombus-formation in various arteries, or by rupture, to similar and often multiple areas of white or red softening.

The areas of softening (encephalomalacia), whether of embolic or local origin, become somewhat rapidly pigmented in case they contain blood. The surrounding yellow zones gradually fade as the lesion grows older, the edema subsides, the loss of substance is only partially made good by organization, and the typical cyst of softening ensues, with its loose-fibered wall and brownish slightly turbid enclosed liquid. The cysts which follow white softening contain a colorless and almost clear fluid.

Aneurysms (preferably in the basilar and Sylvian arteries) occur and may remain undiscovered in the mass of subpial or subdural hemorrhage following their rupture. Miliary aneurysms should be searched for like miliary tubercles by teasing out and washing the vessels (for instance, the Sylvian arteries).

Voluminous hemorrhage (apoplectic) follows rupture of sclerotic arteries in the brain substance. The most frequently affected of the cerebral arteries is one of the lenticulo-striate branches (Charcot's artery of hemorrhage) of the central ganglionic system.

Edema of the brain, flattening of the convolutions, and pressure about the veins follow; in many cases bleeding continues till the adjacent ventricular wall breaks and all the ventricles are speedily flooded. In other cases coagulation interposes, and a smaller local lesion remains which heals more after the fashion of an infarct. The importance of this typical apoplectic hemorrhage in the basal ganglia depends upon its effect on the fibers of the internal capsule. Thus, if the hemorrhage destroys the fibers of the anterior two-thirds of the posterior limb of the internal capsule, that is, resects the pyramidal tract, total hemiplegia of the opposite side of the body is sure to ensue. Smaller hemorrhages may pick out smaller fiber-systems, whereas larger hemorrhages may involve the upper sensory tracts as well as the motor tracts. At the time of the injury the effects of the hemorrhage are magnified by the surrounding edema; if healing takes place, the lesion diminishes in volume and fewer muscle groups and sensory areas are involved than at the outset. Cured or repaired hemiplegies may live for years and die of some intercurrent disease, often related, however, to advancing arteriosclerosis.

Besides voluminous hemorrhage due to arteriosclerosis, the brain and the cord exhibit multiple small hemorrhages in perivascular spaces which are due to manifold causes. Some of them are due to miliary aneurysms, some to sclerotic changes occurring in the distributing system of arteries, some to whatever conditions underlie the hemorrhagic diathesis, some to the toxines of acute infectious diseases (Staphylococcus pyogenes aureus, Bacillus typhosus), some to electric and mechanical shocks, and some possibly to unknown endotheliolysins. Hemorrhages, in part of mechanical origin, occur in leukemia, especially the lymphatic form.

There are few cases in which it is warrantable from brain findings alone to assert cerebral hyperemia or anemia. This is not to say that they do not occur in life.

In this place may be mentioned two diseases of the dura mater which are of immediate importance. Chronic internal hemorrhagic pachymeningitis consists in the successive deposit and organization of layers of hemorrhage in the inner meshes and on the inner surface of the dura. The pigmented membrane or the fresh hematoma may extensively compress the convolutions, shoving them away from the dura *en masse* with a broad wave-like surface. The condition occurs chiefly in old men.

The sinuses of the dura mater are the site of thrombosis. Marantic (autochthonous) thrombosis occurs frequently in the longitudinal and lateral sinuses of the very young and the old and in chlorosis. In the brain follow stasis, edema, hemorrhages, or even encephalomalacia. The seat of infective thrombosis is, as a rule, the lateral sinus opposite the sigmoid fossa of the temporal bone (following otitis media and interna).

Disorders of the lymph circulation are mainly shown in the ventricles and in the arachnoidal villi. Obstructions in the choroid circulation, notably in the vein of Galen, are often attended with internal hydrocephalus; but, as a rule, chronic inflammation or other occlusive change is found lower down in the ventricular system. Such mechanical obstruction at the foramina of Monro, the aqueduct of Sylvius, and at the foramina of Magendie and Mierjejewski will separately produce ventricular dilatation above the point of occlusion, provided that the lymph transudes as usual from the choroid plexuses. Below the lesion (tumor, organization of exudate in healed cases of meningitis and fracture of the base) the lymph flows away unimpeded to the subdural sheath of the spinal cord.

The circulation in the arachnoidal villi is impeded in chronic passive congestion of the sinuses. In certain cases the arachnoidal villi are themselves filled with blood. Their development varies, although irregularly, with age. In old subjects the villi may form a dense mat a few centimeters wide on both sides of the longitudinal sinus. Some villi grow very large and, sometimes devoid of dural sheath, lie in small cavities in the inner table of the parietal bone; such villi have been known to perforate the bone. They must be distinguished from multiple small true herniæ of cerebral substance, which are occasionally seen.

TRAUMA.

The effects of fracture at the base of the skull (more common than vault fractures) are obvious. Laceration of the temporal lobes is frequent. Hemorrhage occurs at the site of the injury, but is apt to be more extensive, through contrecoup, in the tissues of the quadrant opposite to the injury.

The cases of brain hemorrhage without fracture permit more errors in diagnosis. Not every brain hemorrhage in a case of appropriate accident is due to the accident. Fresh hemorrhage from organizing chronic internal pachymeningitis is a somewhat frequent source of confusion; the subject falling from his hemorrhage produces external injuries which favor the diagnosis, fracture. Rupture of Sylvian aneurysm, apoplexy from arteriosclerosis, hemorrhage from encephalitic lesions, may be hastily interpreted post mortem, as sometimes necessarily in life, to be the effect of trauma.

The result of healed fractures of the skull may become manifest after years. A serious outcome is a slowly condensing scar at the base of the brain producing pressure-atrophy of nerve trunks, and in the roof of the fourth ventricle, affording a chance of the onset of chronic internal hydrocephalus. The minuter lesions in laceration of the cerebrum, whether present alone or in combination with actual fracture, may give rise to protracted delirium during healing. After these lesions, which are in the area of the cortical arterial system, are quite healed (cicatrix, gliosis), they may still give rise to epileptiform attacks. In such cases minute gross search is required for healed lesions.

The effects of trauma on the spinal cord are for the most part obvious. In the peripheral nervous system marked retraction may occur from the point of lesion. Cicatrization (interstitial neuritis) may be complicated after amputation by the occurrence of large bulbous masses (*amputation neuroma*).

INFLAMMATION.

Bacteria invade the nervous system and the pia mater by infective emboli (lung, heart valve, general infection), sinus-thrombosis (otitis media and interna, emissary veins), extension through lymph channels (nose, sheath of optic nerve, perivascular sheaths), and direct extension (dura mater and cranium). The animal parasites (cysticercus cellulosæ, echinococcus hydatidosus) are found in lymph spaces or in the ventricles.

The massive abscesses, derived by extension from the middle and internal ear and found in the temporal lobe and the cerebellum, are unmistakable. They are usually due to the pneumococcus, and are often of long standing and encapsulated. The foci of greatest destruction seem often to occur in the little-nourished area of the white matter of the temporal lobe between the termini of the cortical and the ganglionic arterial systems.

No other massive lesions are as a rule confused with otitic abscess. Large solitary tubercles and gummata require microscopic diagnosis. The findings in other organs are important here.

More characteristic are the miliary tubercles found in disseminated tuberculosis, either separately or in the fibrino-purulent exudate at the base of the brain. The miliary and conglomerate tubercles are often found on the Sylvian arteries, in the choroid plexus, and on the cerebellum, but more sparingly in the vertex. The gross differentiation between tuberculous and granular ependymitis is sometimes impossible.

Diffuse lepto-meningitis is unmistakable. The streptococcus may be recovered from what looks like a slightly turbid edema of the pia. The fibrino-purulent type of tuberculous meningitis may resemble, in the absence of careful search for tubercle, an acute meningitis due to the pyogens.

Leptomeningitis due to the meningococcus shows in very acute cases little exudation, except at the base; the surface of the brain is pink, the pia is edematous, and the beginnings of the exudate appear as yellowish lines along the sulcal veins. The exudate later becomes very fibrinous and is most marked as a rule at the base of the brain, in the cerebellar meninges, and near the fissures of Rolando. The spinal exudate is less in the pia than in the subarachnoid space and is most marked posteriorly. The fluid of the ventricles is increased and cloudy; the ependyma soft, lusterless, uneven. The exudate is apt to extend along the optic, trigeminal, facial, and auditory nerves.

The lesions of leptomeningitis due to the pneumococcus, staphylococcus pyogenes aureus, and streptococcus are rarely so extensive as the meningococcal lesions. The cord is not so extensively attacked, and the nerve roots are spared. Microscopic examination is necessary to distinguish all the forms, with certainty.

Whereas massive abscess and various types of leptomeningitis are grossly striking, it may be hard to distinguish clearly the smaller lesions of acute diffuse encephalitis, meningo-encephalitis, and ependymitis. The small pyogenic abscesses (ineptly likened to flea-bites) may be hard to tell from perivascular hemorrhages. The larger pinkish edematous areas are often confused with areas of encephalomalacia of embolic or thrombotic origin.

The pyogenic abscesses are in fact often hemorrhagic. Bacteria (Staphylococcus pyogenes aureus, Bacillus typhosus) sometimes occasion extensive hemorrhages in the cerebral substance, which may break into the ventricles and present the picture of an apoplexy of arterio-sclerotic origin.

The gross picture of chronic leptomeningitis is well defined. The vertex rarely shows more than small linear plates of thickening over sulcal veins. The tissues at the base show considerable thickening. In many cases the openings in the roof of the fourth ventricle have become occluded by scar tissue, the outcome of organization of exudate there. A frequent outcome of this occlusion, favored by chronic changes about the choroidal vessels, is dilatation of the third and lateral ventricles (chronic internal hydrocephalus).

Changes in the cortex beneath the exudate in cases classified as leptomeningitis, although grossly invisible while acute, can give rise to small adhesions which prevent the pia from stripping readily.

Similar cortical adhesions of great number and extent are found in the brains of general paresis of the insane. Earlier stages may be seen in tuberculous meningitis and in syphilitic meningitis.

Adhesion between dura and pia occurs seldom (except where normal about transarachnoidal vessels and arachnoidal villi); it may occur in extensive trauma, over tumors, and as a healed syphilitic lesion.

The dura mater of children is adherent to the calvarium. Old subjects often show adhesions of varying extent over the vertex opposite the bregma (chronic adhesive pachymeningitis). The dura of the cervical region of the cord is at times locally much thickened, so as to resemble a fibrous tumor; the chronic inflammation involves also the pia mater, the nerve roots, and even the cord septa (*pachymeningitis cervicalis hypertrophica*). The origin of the process is doubtful.

INTERPRETATION OF GROSS APPEARANCES.

It is difficult to interpret the gross appearances of the nervous system in disease. The visible and tangible data in the peripheral nervous system are confined to solutions of continuity, frank atrophy, interstitial neuritis, and involvements by extension from other lesions; many of the most essential changes escape detection. Relatively more can be seen by gross methods in the retina than elsewhere at the periphery. The data of muscular atrophy and apparent hypertrophy should be considered amongst peripheral data.

The gross data of the central nervous system permit in part immediate and certain interpretation. Thus the solutions of continuity in the brain and cord, voluminous effects of vascular disease (sclerosis, aneurism, hemorrhage), massive abcesses, many cases of acute and chronic meningitis, the effects of heightened intracranial pressure, edema, internal hydrocephalus, certain tumors, and various aplasias and maldevelopments permit diagnosis on inspection.

Another series of data becomes clear when considered together with findings elsewhere in the body: thus metastatic tumors, the results of pyogenic and other infections, tubercles, gummata.

There is a great residuum of cases in which the diagnosis must be left in doubt from gross findings. As an example may be cited the diagnosis of glioma. Experience shows that little can be told from the site, size, shape, color, consistence, and other gross characters of a tumor-like mass in the brain, what kind of tumor it may be, or even whether it be a tumor. Brain tumors have in the gross been confounded with tubercles, with gummata, with lesions in a stage of repair, and with areas of hemorrhage, and contrariwise. And tumors have been found microscopically where no tumor was expected from gross appearances. The gross diagnosis of glioma is often successful, but only because gliomata are common. It is, in general, hazardous to predict glioma from gross appearances, and equally hazardous to predicate anything else in the test case.

It is hard to lay too much stress on the mistakes of diagnosis produced by the artefacts made in removal and inspection of the nervous system. The mistakes due to this cause extend into the region of microscopic diagnosis. The fascicular structure of many parts of the nervous system readily permits the most varied and gross translocations of tissue and apparent heterotopiæ which are not interpretable in microscopic sections. Moreover, the size and heterogeneity of nerve cells make them easily accessible to apparent lesion through artificial pressure. Post-mortem changes are of less importance in this matter, although the data as to consistence are disturbed. Then follows a series of artefacts produced, like many in other organs, by the fixatives employed. Reliance is nowadays placed upon total immersion in a solution of formalin or upon various methods of embalming the nervous system in situ. The results and the extent of some lesions are well studied in this way. Many data concerning causes are, however, lost.

III. MINUTE LESIONS OF THE NERVOUS SYSTEM.

METHODS OF EXAMINATION.

The pia mater, vessels, and connective tissues are examined by the methods employed for other organs. Fixation in Zenker's fluid, paraffin imbedding, and staining with methylene blue and eosin form a good method at the outset. The staining with methylene blue and eosin is supplemented by the aniline blue connective tissue stain (Mallory). Arteriosclerosis is so large a factor in many lesions that the elastic tissue stain of Weigert must frequently be used.

For the study of the neuroglia and ependyma, fixation in Zenker's fluid permits the use of the phosphotungstic acid hematein method (Mallory). Weigert's stain for neuroglia may be employed. These methods will not succeed unless the tissue has been fixed within a few hours post mortem. Fibrin stains and the iron hematoxylin method may be employed. The study of the cell bodies of neuroglia cells is best carried on in sections stained with methylene blue and eosin.

The study of the nerve cells may be adequately made with sections stained with methylene blue and eosin after fixation in Zenker's fluid. Excellent work is done with the classical method of Nissl (alcohol fixation, staining with methylene blue soap solution), and, for work on nerve cells which depends for interpretation on comparative studies in the literature, Nissl's method should be used. The manifold methods used by histologists in making clear the structure of the nerve cell are unfortunately of little avail in pathological work, as their results are too precarious or require perfect fixation or are by their nature capricious. The Golgi method, for example, yields few usable data in neuropathology.

Work upon the adnexa of the nerve cell will, as a rule, require fixation in formalin. The data of fatty degeneration are gotten by the Marchi method. The presence or absence of the myelin sheath is determined by Weigert's method for myelin. The axis cylinder and its fibrillæ are as yet scarcely accessible to extensive pathological work. The presence of axis cylinders can be made out by the use of several of the methods mentioned above.

The methods employed fall into two classes according to the desire of the worker to study — on the one hand the cause and nature of the lesions, on the other hand the extent of their effects. It is the effects in tract degeneration which, as a rule, engage neuropathological attention.

PIA MATER AND CONNECTIVE TISSUES.

The thickness, texture, and closeness of attachment of the pia mater should be noted. Judgments of thickness must be modified with the direction of the section, as planes tangential to the cortex cut broader areas of pia. Thickening is usually best marked in the outer layers. The cells of exudations resemble those elsewhere, save that the pigment-bearing or cell-containing phagocyte occurs very early in large numbers. The phagocytes accumulate in lesions of the most varied origin. Mitoses in endothelial cells are found. The forms known as compound granule cells are frequent, containing various products of degeneration of cell, fiber, and myelin.

In acute lesions the amount of edema and fibrin varies greatly. The amount of edema of the pia depends somewhat on the degree of internal hydrocephalus. There is considerable fibrin in exudates due to the meningococcus and the pneumococcus. The intima of the arteries shows proliferative changes in syphilitic, tuberculous, and pneumococcal meningitis, more rarely in other forms.

In chronic lesions the collections of lymphoid and plasma cells about the vessels, especially about the veins, become prominent. These collections are characteristic only in combination with other lesions, such as tubercles, gummata, and the destructive nerve cell changes and proliferative glia changes in general paresis.

About the smaller vessels in the cortex it is noteworthy that the plasma cells readily assume a flattened shape.

Many hardening fluids cause apparent dilatation of perivascular spaces, resembling similar spaces about nerve cells.

NEUROGLIA AND EPENDYMA.

The cells of the supportive neuroglia have round or oval nuclei according to their situation among loose or stratified fibrillæ. The cell bodies are scarcely evident either in normal supportive neuroglia or in the overgrown neuroglia in a reparative or compensatory lesion (lining of old cyst of softening, posterior columns in advanced tabes dorsalis). In stains for intercellular substance (Weigert's or Mallory's neuroglia stains, Mallory's aniline blue connective tissue, iron hematoxylin) the fibrillæ are shown to be everywhere free from the cells, which appear as free nuclei, crossed and recrossed by separate fascicles of straight or smoothly curving fibrillæ, each of one diameter throughout. The number of fibrillæ to a cell is indefinite; it is usually impossible to say whether or not a fibrilla belongs to a given cell. The number of fibrillæ, and to a certain degree the number of corresponding nuclei, is normally greater in the sulci than over the surfaces of the gyri. In the subpial layer of the cortex cerebri it is difficult to estimate the thickness of neuroglia to be termed a lesion. False estimates based on sections made through shallow sectors of cortex must be avoided. There is an increase of thickness of the subpial glia with advancing age.

Where the neuroglia is still actively growing the cell bodies are visible. The nuclei may be larger and clearer, and are, as a rule, eccentrically placed in the cell. Two or more nuclei are not seldom found in a cell. Where the fibrillary intercellular substance is not too dense, the cell bodies may be seen to have processes, so that the cells roughly resemble ganglion cells. The cell bodies are, however, homogeneous and contain no granules. The cell processes are often branched and end bluntly. Along their edges may occasionally be seen fibrillæ which are apparently in the act of separating from the cell. It is such cells which, from their appearance in Golgi impregnations, have been termed spider cells.

In the nerve cell layers the neuroglia cells are rarely found increased without corresponding changes in the nerve cells. Sometimes in the cortex in general paresis the neuroglia cells far outnumber the nerve cells. The age of foci of gliosis can be roughly told from the presence, in acute lesions, of mitotic figures, multinucleate cells, and cells with branching processes; in later lesions of cells with fibrillæ apparently in the act of splitting off from processes, and cells with smaller cell bodies in whose neighborhood the fibrillæ outnumber the processes, and, finally, of fascicles of fibrillæ in which relatively few apparently free nuclei are imbedded. The mitoses of endothelial cells, so frequently found in destructive brain lesions which are still active, may sometimes be confounded with true neuroglia mitoses. In the pineal body, in places where the neuroglia abuts upon non-nervous tissue (adventitial and pial connective tissues) in gliomata, at the edges of old cysts of softening, and occasionally elsewhere, much larger and strap-shaped fibrillæ are found. In appropriate places these fibrillary masses may be shown to fray out at the ends like cut wire rope. Some of the structures described as neuroglia feet applied to vessels can be resolved into such structures.

The ependyma is often desquamated, especially from the tops of the elevations in granular ependymitis and in edema of the ventricular walls. Over areas from which the ependymal layer has been absent for some time there occur focal fibrillary overgrowths of neuroglia. With advancing hydrocephalus these focal accumulations of cells and fibrillæ condense and are projected farther and farther beyond the ependyma layer to form the grossly evident granules of granular ependymitis. This condition is perhaps wholly a mechanical effect. It occurs in arteriosclerosis, cardiæ, and cardiorenal diseases, as well as in tuberculous meningitis and local brain diseases with increase of ventricular fluid.

Below the ependyma there occur in many diseases, but especially in epidemic cerebrospinal meningitis and in tuberculous meningitis, characteristic multinucleate structures, in whose cytoplasm may be light areas containing numerous dots or short rods which assume the neuroglia stain. Similar structures are seen in the neighborhood of the central canal of the cord, and here numerous fibrillæ run in close apposition to the cell walls.

NERVE CELLS AND ADNEXA.

The nuclei and bodies of all nerve cells may exhibit a series of changes resembling those of the parenchymal cells of many other organs. In the larger cells, which show Nissl granules, these changes become striking. In the axis cylinder, myelin sheath, and pericellular structures, there is a series of lesions having few analogies elsewhere in the body.

As to general nerve cell hypertrophy there is no evidence. Atrophy is observed in a variety of chronic diseases, both vascular diseases and some not evidently vascular. Simple atrophy may be made out from small size of the cell, more deeply re-entrant angles between dendrites, apparent increase of autochthonous pigment, absence of dendrites, or absence of axis cylinder connections. In higher grades of atrophy the cell body stains densely (pyknosis) ; but pyknotic or chromophilic cells are often artefacts and, at any rate in human material, do not signify general atrophy. Atrophic cells may become calcified.

Nerve cells undergo *cloudy swelling*, which may be shown by their contours alone, when well-defined swellings appear between the bases of the dendrites. Cloudy swelling is distinguished from *fatty changes* if the granules clear up on the addition of acetic acid. Frozen sections may be stained with Scharlach R. The pigments assume a red which is much less intense than the red given by fat in Scharlach R.

Besides cloudy swelling and fatty changes, nerve cells at times show a degenerative change in which the cell body seems to consist of coarse dust-like granules. In certain cases these granules are fibrinoid, and stain with methods for fibrin and neuroglia.

Vacuolation may be present due to collections of fluid or of colloidal substances. The effect of reagents must be rigidly excluded for the strict diagnosis of vacuolation.

The nucleus may undergo in the course of cell destruction the process of lysis, rhexis, pyknosis, quite as with other cells. Karyokinesis has not been observed. Occasionally there is seen a dense refracting mulberry-like nucleolus, doubtless an artefact.

Besides the relative increase of cell pigment seen in atrophy there occurs an absolute increase of pigment, which may lead to cell degeneration.

In those cells which have large cell bodies containing Nissl granules, and especially in the larger somatochrome cells, there is a series of lesions marked by changes and disappearance of the granules. The granules may become dissolved or fail to stain near the nucleus (central chromatolysis) or in the cell periphery (peripheral chromatolysis) or throughout (total chromatolysis). The granules may undergo dust-like transformation, may fragment, or may be apparently swollen.

These granule changes, although described as specific, are no more specific in various brain and cord lesions than are the more general changes in nerve cells. The whole cell picture must be considered. Of definite and consistent cell reactions, the best example is the axonal reaction (tertiary degeneration) of the nerve cell, which is a rapid outcome of separation or destruction of its correspondent nerve fiber. In the axonal reaction the Nissl granules (of an anterior horn cell, for example, directly after resection of corresponding nerve) fall into fine particles or become dissolved, and permit the nucleus to assume a mural position or sometimes to indent the wall. This condition is often perfectly curable, but may in some cases lead to atrophy.

Marked but curable changes are brought about in fever — swelling of cell and dendrites, disappearance of Nissl granules, with transformation into very finely granular material, disappearance of nuclear outline.

The most celebrated of the alleged changes is the *acute Veränderung* of Nissl. In a case showing this alteration, according to Nissl, every nerve cell of the cortex is swollen. The nuclei are enlarged and round (the normal nucleus of a pyramidal cell is slightly oval). The nucleoli are dark, but contain light points. The Nissl granules fail to stain, or cling as small plates to the nuclear membrane. The cell bodies stain faintly; their borders are indistinct. The dendrites are stained for longer distances than is normal; their bodies are indistinct. The axone hillock, however, stains (contrary to the normal condition) and stains sharply. It is best for comparative purposes to employ Nissl's original method for nerve cell work.

The pericellular net and the neurofibrillæ are brought out quite capriciously with accessible methods. No lesion can be argued from their absence. The pericellular region may show an increase of satellite cells, rarely polynuclear leucocytes, and coagulum. The satellite cells are at times increased in number and may indent or occupy spaces within nerve cells (so-called neuronophagia, neuronoclasia). Deeply staining incrustations are occasionally found on the nerve-cell borders.

With the other adnexa, *i.e.*, the axis cylinder and myelin sheath, the lesions are more definite than in the pericellular net and the intracellular fibrillæ. The axis cylinder and the myelin sheath, as a rule, undergo destruction together. Only in the classical "sclérose en plaques" (multiple sclerosis of adults) do the axis cylinders preserve function in the absence of myelin investment. Just as the nerve cell exhibits a typical axonal reaction on separation from its fiber, so the fiber undergoes degeneration when separated from its cell. The swelling and fragmentation of axis cylinder and varicosities and fatty degeneration of myelin sheath attack the fiber distal to the point of injury and for a short distance proximally. The local destruction due to the trauma (traumatic degeneration) is succeeded in a short period by a secondary or paralytic degeneration of the part separated from the correspondent nerve cell.

MALDEVELOPMENT.

The cells of ill-developed brains differ from the cells of brains which have been subject to lesion by the absence of scar tissue, and gliosis. Nevertheless the injuries may be wrought so early in life that well-marked gliosis is not yet possible. In such cases, for instance in porencephaly, it may be impossible to distinguish from an examination of the cells whether the lesion is the effect of maldevelopment or early lesion. The brains of old idiots form the most fruitful material for study of these conditions. It is sometimes possible in these brains to secure fair imitations of the cortex of lower animals. The cellular structure of the human fetal brain of various stages is reproduced in some cases.

Another series of maldevelopment cases shows not merely absence of parts and stoppage of cell development, but actual distortions and heterotopia of structures. An instance of this is the formation in malformations of the cerebellum of islands of cells resembling Purkinje cells, but without processes, surrounded by a few cells resembling those of the granular layer.

CIRCULATORY DISORDERS.

Anemic necrosis in the brain and cord is of the colliquative form. The dead tissue softens and swells into a mass of gray detritus which may be variously colored by blood. The detritus contains considerable myelin or material staining with osmic acid. Hemosiderin and iron-free pigments may occur in the area. Granule cells rapidly appear, to aid in absorption.

Very small areas of colliquative necrosis may become thoroughly organized. The rule is partial organization, with cyst formation.

The cyst fluid may be yellowish or brownish and slightly turbid, containing numerous fatty granule cells. The walls are uneven from the jutting in of vascular tufts surrounded by coarse and fine neuroglia fibrillæ. The older lesions show a slowly condensing capsule of neuroglia, with fewer and fewer neuroglia cells of the type in which cell bodies are evident.

Small hemorrhages into the brain substance are characteristically linear, dissecting the perivascular sheaths or running between fiber fascicles. In the clot hematoidin crystals and hemosiderin are demonstrable. Dissolved iron-containing pigment may be reprecipitated for a considerable distance from the original extravasation. Phagocytes are found containing blood globules and pigment. Reabsorption of perivascular hemorrhages is rapid; but pigment-bearing phagocytes are demonstrable long after the injury. The process of healing in destructive hemorrhage resembles that of anemic necrosis. Occasionally there may be found in the destroyed area dying nerve cells, whose shrunken bodies contain granules smaller than Nissl granules, and staining by methods for neuroglia and fibrin.

Periarterial overgrowth of neuroglia may be found in cases with normal vessels, in arteriosclerosis, and in gliomata.

Hyaline degeneration is found in the media of small vessels in the brain and in the meninges in tuberculous meningitis and other conditions. This may be hard to distinguish from caseation. Some of these areas are partly calcified.

The intimal changes of arteriosclerosis are frequent. Subendothelial proliferation of intimal cells occurs in tuberculous and pneumococcal meningitis. Rapid and extensive intimal proliferation in meningeal vessels is characteristic of syphilitic meningitis.

INFLAMMATORY LESIONS.

The ending "-itis" is extensively used in describing lesions of the nervous system of quite various origin (thus alcoholic polyneuritis, compression myelitis, parenchymatous-degenerative myelitis, granular ependymitis, traumatic, toxic, and bacterial encephalitis). The ending "-itis" *as used* virtually means "lesion of."

The course of exudation and repair in the nervous system exhibits peculiar features. The passage of fluid from the vessels is peculiarly swift and voluminous; and the edema may at times be remarkably transient. Diapedesis and small perivascular hemorrhages are frequent. The exudation of polynuclear leucocytes, though even and voluminous in the meninges, is somewhat rare in the brain substance itself except in large destructive lesions and in areas softened by edema. The most characteristic cell of various brain lesions is the large phagocytic or compound granule cell which accumulates often in extraordinary numbers about vessels and in cysts of softening. Many of these cells are of endothelial origin; mitoses are often demonstrable near vessels.

Besides the changes in and about the vessels, which nerve tissue shares with other tissues in inflammation, there are changes in the neuroglia of the central nervous system in inflammation. Upon the density of the subpial neuroglia may be dependent the slight penetrative power into nerve tissue which polynuclear leucocytes show. If this subpial glia is dissolved by local lesions, as in epidemic cerebro-spinal meningitis, the leucocytes wander considerable distances from the pial vessels. The leucocytes wander readily in either direction through an apparently intact ependyma. The neuroglia cells in the cortex and beneath the ependyma are increased in number. Mitoses in the glia are demonstrable in favorable cases. Neuroglia cells with large cell bodies, one to several nuclei, and branched processes are frequent. The cells may be so abundant, in cases of epidemic cerebrospinal meningitis, as to outnumber the ganglion cells.

In repair the neuroglia cells pass through the usual series of changes leading to new fibril formation. In case there is no destruction of vessels, the outcome of the process will be an accumulation of neuroglia fibrillæ which at first slowly contracts, but finally remains stationary. The fibrillæ abut endwise upon the vascular adventitia. As they approach the pia they assume two relations thereto: the majority of the fibrillæ are tangential, but a number of parallel fibrillæ touch the pia endwise, sometimes fraying out. The glioses in the lower cell layers are less regular in appearance. By irregular contractions the normal radial arrangement of the nerve cells is distributed. An irregular disposition of glia nuclei can sometimes be noted between the fibers of the white matter.

Acute inflammation of the pia mater is almost necessarily attended with effects upon the substance nourished by the membrane. Pyemic abscesses of cerebrum and cerebellum are also frequently accompanied by pial lesions. Massive abscess is often found without pial lesion; nor is the relation by veins or lymphatics to the ear always demonstrable, even in temporal abscess with coexistent inflammation of the middle ear.

Pyemic abscesses are often hemorrhagic, although lesions in the blood vessels are not always demonstrable. The hemorrhages appear to originate often in the neighborhood of the layer of large pyramidal cells.

REPAIR AND REGENERATION.

The peripheral nervous system exhibits remarkable reparative and regenerative processes after injury. The processes of degeneration following injury are the same as those exhibited by the central nervous system. Thus, besides the local degeneration due to trauma, a characteristic secondary degeneration affects the axis-cylinders and myelin sheaths for their total length distal to the injury. This secondary or paralytic degeneration affects also the central stump as far at least as the first nodes of Ranvier above the point of lesion. The sequel to the secondary degeneration of peripheral nerves, however, differs notably from the slow gliosis which follows secondary degeneration in the central tracts. The peripheral nerves after injury tend to regain function by complete regeneration of their axis-cylinders and myelin sheaths. Anatomically the peripheral nerves differ from central nerve bundles in a lack of supportive neuroglia and in the presence of the sheaths of Schwann.

It is not clear what brings about the regeneration of the conducting elements; it is doubtful whether the axis-cylinders simply repeat in regeneration the course of embryonic growth by growing outward from the point of lesion, or whether they are laid down peripherally by the aid of adjacent elements.

Active proliferation of the cells of the sheaths of Schwann is shown as early as the fourth day after injury, at a time when the fragmentation of axones and myelin is still marked. The regeneration of the axis cylinders follows slowly. The regeneration begins centrally, and where growth is not obstructed proceeds roughly at a rate of one millimeter a day toward the periphery. This direction of growth repeats the embryonic direction, but no similar regeneration takes place into the spinal cord after resection of dorsal roots adjacent to the cord. Peripheral regeneration is favored by the presence of the corresponding motor and sensory cells. The autogenous regeneration of axis cylinders described as occurring in young vertebrates independently of the correspondent nerve cells yields a partial, but never permanent, restoration of function. A regeneration of peripheral nerves, in every sense complete, is effected by a distal new growth of axones and myelin sheaths which is earliest demonstrable in areas nearest the lesion. The axis cylinders of the central stump tend in growing out to split into bunches of smaller fibers. The rate of regeneration depends largely upon the initial character of the traumatic changes. The distance to be travelled by the axone fibrils and the varying density of the cicatrix make it impossible to assign the time of recovery within months. The most convenient tubular path seems to be chosen by the regenerating axones which grow along threads or through hollow objects inserted in the tissue. This tendency is turned to account in the surgical suturing of nerves, wherein reversed segments of the nerve itself are employed to effect union over wide gaps. After amputation curious painful tumors (" amputation neuromata ") are occasionally produced by irregular and ineffectual regeneration of axis cylinders within the scar.

In the healing of nerves there is (1) a local scar formation following the traumatic degeneration, and (2) a neurotization of the scar by distally-growing axones, and finally (3) complete regeneration of the distal portion of the nerve. Secondary degenerations in the central nervous system, on the contrary, are healed not by axone regeneration but by gliosis.

PRIMARY DEGENERATION.

The term " primary " not only cloaks ignorance of the cause, but also is frequently applied to conditions of which the early stages have never been observed. Primary degeneration, whatever it be, is contrasted with secondary (paralytic or Wallerian) degeneration, and this in turn with the tertiary degeneration of nerve cells after peripheral injury.

As a rule, however, the term " primary degeneration " is used, not of effects wrought in separate cells, but of effects going forward in several tissues, such as nerve-cells, glia, and sometimes the connective tissues. The effects seen in the glioses of tabes, general paresis, and multiple sclerosis of adults cannot in part be distinguished from the phenomena of repair. In some diseases examined, early signs of the process of degeneration may be found in nerve cell changes, fragmentation and solution of axis cylinder, varicosities, and fatty change in myelin sheaths. But these active changes differ in no point from degenerations whose causes are known.

NEW GROWTHS.

Besides secondary tumors, of which the brain is a frequent site (from *breast cancer*, *malignant chorio-epithelioma*, *melanotic sarcoma*), the nervous system exhibits characteristic primary tumors. The most frequent primary tumor is the glioma which may be soft and cellular (*glioma molle*), hard and rich in fibrillary intercellular substance (*glioma durum*), or supplied with cysts and ependyma-like collections of cells (*ependymal glioma*). Multinucleated cells and cells roughly resembling ganglion cells occur in many examples of glioma. It is not clear that these types are genetically separate. The gliomata of the brain are, as a rule, single, grow by infiltration in nerve tissues (sparing both membranes and cranium), and tend to interstitial hemorrhage and necrosis. There is no evidence that the glioma produces a toxine. The malignancy of gliomata depends on their situation.

Very large tumors develop, often without symptoms, from the dura mater (*endotheliomata*), grow by expansion inwards, shelling out smoothly from deep spheroidal pockets in the cortex. The tumors often contain considerable masses of lime and then constitute the most frequent variety of psammoma.

Sarcomata of the brain (excepting those developed from membranes or cranium) are rarer than has been supposed. The older accounts, in which no study was made of the intercellular substances, form no good basis of statistics. Tumors of the fibrosarcoma group are the commonest variety of sarcoma found.

Cholesteatomata (pearl tumors) are epidermoid tumors, as a rule in close relation with the pia mater or the choroid plexus. They are composed of dead and dying epithelial cells, which are often mixed with cholesterin crystals and accumulate indefinitely. The tumors are dangerous from their site.

The psammoma (tumor containing lime concretions) is a frequent tumor of the choroid plexus, and occurs also in the brain substance and in the pineal body. Microscopic examination is required to tell whether a psammoma belongs to the sarcomata or the gliomata.

Other primary tumors occur. The most prominent of these are angiomata of several types and sarcomata of the type secreting intercellular substances, developed, as a rule, from the meninges.

The *chordoma* is a small tumor which develops from the remains of the chorda dorsalis at the spheno-occipital synchondrosis. The tumor lies at first outside the dura, but later may push its way beneath and attain the size of a cherry. The tumor is mucoid in consistence. There is a homogeneous intercellular substance. The cells are highly vacuolated.

Neurofibromata are fibrous tumors developing from the interstitial tissue of peripheral nerves. Sometimes the new growth takes place from the endoneurium, in which case the nerve fibers run separately through the tumor. Sometimes the perineurium is the starting-point of the growth, in which case the nerve bundle runs through the middle of the tumor. In the larger tumors nerves may no longer be demonstrable. The size of the new growth is not in proportion to the size of the nerve bundle from which it develops. Similar tumors may develop from other structures than nerves.

The spinal cord shows various tumors of the types seen in the brain. The condition known as *syringomyelia* may be grouped with the new growths or with the maldevelopments. In syringomyelia fusiform cavities are found, as a rule in the cervical cord, related with the central gray substance, often of the posterior horns. The cavities are lined with edematous neuroglia and are thus contrasted with the cavities lined with ependyma found in hydromyelia (a dilatation of the central canal analogous to internal hydrocephalus). The origin of syringomyelia is unknown, but probably manifold. Certain cases yield typical clinical pictures.

On account of the number of tissues which go to make up or may be included in the nervous system, few diagnoses of primary tumors can be rendered without resort to methods for demonstrating intercellular substances as well as the cell forms.

IV. DISEASES PECULIAR TO THE NERVOUS SYSTEM.

The central nervous system consists of parallel and interlacing tracts of medullated fibers and of voluminous gray centers interposed between the termini of the tracts. The fiber tracts permit linear conduction only, whereas the gray centers effect, besides an end-to-end conduction between tracts, also multiple cross-conductions, in virtue of which indirectly any two tracts may be made to intercommunicate.

Although the nervous system throughout presents this fascicular structure, yet the bundles are far from being on one level of importance. It is conceivable that no single fascicle of the central nervous system is essential to the performance of its functions, on account of the manifold switching of impulses made possible by cross-conductions through the gray centers. Moreover there is one great group of fiber fascicles which may be quite cut out of function without impairing vital activities — the association tracts of the brain. In fact, in the lower orders of animals no such system is developed.

To the great group of association tracts, which appear to form a specialized apparatus for elaborate cross-conductions between gray centers, may be opposed the group of fiber fascicles known as the projection system (motor and sensory tracts). The fascicles of the projection system are interposed, not between gray center and gray center, but between skin and voluntary muscles or between eyes and glands or between mucous membranes and the sympathetic system, and so on. The fascicles of the projection system serve to unite functionally various non-nervous structures. For a complete projection system but one loop is theoretically necessary with a center for inter-communication. As it happens, however, in man and the higher animals various gray centers are interposed at lower levels, forming shorter loops. These various fascicles between centers are subject individually to disease; and the different combinations of disease which are for some reason confined to the tracts and centers are known as system diseases. The system disease is then, in a sense, a focal disease of the nervous system; but the foci are linear, extensive, not related wlth the distribution of the arterial tree, anatomically and physiologically well-defined. The neurone theory has been offered as the key to an explanation of these diseases. I have here presented the diseases objectively.

Focal injury to the adult nervous system produces more than focal effects. Remote regions are rapidly involved in what has been termed a secondary degeneration. In a case of focal lesion the tracts showing secondary degeneration will be characterized as follows:

1. The degenerated path runs out of the region of injury and is proportional in number of fibers to the elements of the destroyed area.

2. The area of degeneration does not spread by contact in its course with other areas. In case the degenerated path splits, the total cross-section of degenerated fibers remains the same and the area between remains intact.

3. The process of degeneration shown is at the same stage throughout the degenerated path.

4. The changes in the gray center corresponding will affect only the appropriate cells. Cells of various dignity will not be involved by reason of contiguity.

It is evident, therefore, that regular and systematic remote changes are wrought by destruction of isolated parts of the nervous system. Similar extensive changes of the same general character are found in cases where there is no evidence of destructive lesion of isolated parts of the nervous system. The cause of these extensive fascicular diseases remains unknown. In many examples the history indicates a slowly acting cause. Older writers were content with the degenerations as primary or idiopathic. Modern writers mention poisons elaborated within the body, the persistent toxine of syphilis, or a combination of these as causes for certain forms. A group known as the combined system diseases has been related with pernicious anemia. Repetitions in successive generations have been noted in some forms. The group as a whole scarcely differs qualitatively or presents different logical problems from various chronic diseases of other organs. The peculiarities of the group are the extent of the lesions, their apparent caprice of development at various foci, and the delimitation and constancy with which various functions are modified or removed thereby. Therefore, it has been said, the triumphs of neuropathology lie in applied solid geometry.

Some effects of lesion in various foci are first considered, and the well-marked system diseases follow:

SECONDARY DEGENERATIONS.

1. Cerebral Palsy of Children.

Extensive lesion, such as acute hemorrhagic encephalitis of the Rolandic region, produces as a rule in children convulsions followed by a hemiplegia or unilateral paralysis of the arm and leg, or of the arm, leg, face, and possibly the tongue. Stable contractures or spastic innervation (tendency to tonic contractions in lieu of movement) of the muscles follow. Characteristically also occur associated movements, athetosis (slow, successive contractions of muscle groups, with extension and flexion, adduction and abduction, at short intervals), a degree of imbecility, and a tendency to convulsions on the paralyzed side.

At autopsy the cortico-spinal motor tract will be found degenerated. At successive levels this tract occupies, first, a part of the converging coronary or tegmental radiations of the centrum semiovale, next, the anterior two-thirds of the posterior limb of the internal capsule, and, now as the pyramidal tract, the middle ventral portion of the foot of the cerebral peduncle. In its course through the pons and medulla oblongata, the various bundles corresponding with the cranial nerves diverge to the raphe, decussate, and come into relation with their respective cranial nerve nuclei. The fibers of the corticospinal tract itself continue to the (incomplete) decussation in the medulla. The degeneration in the spinal cord will then be seen in large part in the pyramidal tract of the opposite side, but in small part also in the direct pyramidal tract.

Cerebral Monoplegia and Cortical Epilepsy.

Under the head "cerebral palsy of children," the frequent cause mentioned was hemorrhagic encephalitis. A similar hemiplegia due to cortical lesion fails to occur in the adult. In the adult inflammatory lesions of the cortex are likely to be so extensive as to produce more general signs than hemiplegia; or, if small, experience shows that the signs produced are of limited range. A destructive lesion of the motor cortex produces some form of cerebral monoplegia or paralysis (without atrophy) with contracture and increased deep reflexes of the limb or muscle groups involved. If the lesion be not destructive, but leave the gray center in a state wherein its functions are performed abnormally, a local form of epilepsy (cortical or Jacksonian epilepsy) is produced, characterized by unilateral spasms (bilateral in the case of muscle groups which normally act bilaterally).

Just as in the cerebral palsy of children, a variety of lesions may produce in the adult the local signs of cerebral monoplegia or cortical epilepsy; but in the latter, perhaps the most frequent cause is new growth, though trauma and inflammatory lesions are often found.

In the case of cerebral monoplegia the degenerate tracts may be followed down in the corticospinal tract sketched under cerebral palsy of children. The coronary radiations from the cortex are slowly shifted in their downward course, so that in the cerebral peduncle the fibers from the frontal cortex come to lie internally and the temporal and occipital fibers come to lie externally with the motor or pyramidal tracts set between.

Cerebral Hemorrhage.

Apoplexy, or cerebral hemorrhage par excellence, is most often due to rupture from disease of a branch of the anterolateral group of the central ganglionic arterial system (branch given off frequently from left middle cerebral artery). The corticospinal motor path becomes degenerate in the cases which recover. Over and above certain general symptoms, the main result is hemiplegia of the side opposite to the hemorrhage. Considerable gradual restriction of the number of muscle groups affected is the rule. Contractures set in, as in the case of cerebral palsy of children and cerebral monoplegia, and atrophies of the correspondent limbs are equally absent. The aphasia, which complicates extensive left-sided hemorrhage, is likely slowly to disappear.

Diseases of the Pons and Bulb.

Glossopharyngolabial (bulbar) paralysis is a name given to several types of disease (the so-called progressive form of beyond middle age, a hereditary form found in children, an acute apoplectic form, a compression type from new growths). It is obvious that small lesions of various nuclei will produce appropriate loss of function and degeneration in appertaining tracts. In the bulb the tracts and the centers are collected into very small compass, so that a lesion the size of a pea may cause bilateral paralysis of, for example, the twelfth nerves. A lesion placed beside the pyramidal decussation produces crossed hemiplegia, involving the fibers of the motor tracts of one side above the decussation and tracts of the other side below the decussation. Contralateral hemiplegia ensues upon lesion above the decussation just as in cerebral palsy of children or in the classical cerebral hemorrhage; but, inasmuch as the destructive lesions must be much smaller so to single out limbs or muscle groups, the history and clinical pictures are likely to be different. These local pontine and bulbar diseases are apt to be chronic. An exception is the form clinically known as the acute apoplectic form, due to basilar thrombosis or to encephalitis (acute polio-encephalitis inferior). Acute hemorrhagic encephalitis confined to the central gray of the floor of the third ventricle and the Sylvian aqueduct (acute hemorrhagic polio-encephalitis superior of Wernicke) produces a bilateral ophthalmoplegia, termed nuclear, with correspondent secondary degenerations in the oculomotor paths in chronic cases.

TRANSVERSE LESIONS OF THE SPINAL CORD.

Transverse lesions of the spinal cord produce pictures of degeneration which differ somewhat at various levels, but have several features in common. Thus, near the plane of lesion, total degeneration of ascending, descending, and commissural tracts is found. At various levels remote from the transverse lesion the tracts degenerate according to a general principle, viz., the motor conducting paths *in general* degenerate downward, the sensory paths *in general* upward.

Below the plane of lesion the pyramidal tracts degenerate, as in the series of lesions just described (cerebral palsy, hemorrhage into internal capsule). In transverse lesions of the upper cord both the crossed and the direct pyramidal tracts degenerate below the plane of lesion. But, inasmuch as the direct pyramidal fibers have all decussated by the middle or lower thoracic segments, below that level the descending degeneration is confined to the crossed pyramidal tract.

Above the plane of lesion (1) a portion of the fibers of the posterior columns degenerate, but, on account of fresh accessions of uncut fibers from higher posterior roots, the area of ascending degeneration continually shifts inward, occupying the column of Goll. (2) The direct cerebellar tracts are degenerated in transverse lesions of the cord which are high enough to cut off the connections between this tract and the cells of Clarke's gray column, which is developed in the median gray of the thoracic cord. But in transverse lumbar lesions the direct cerebellar tract is naturally at no point degenerate.

Of the other tracts of the cord a variety of interesting facts are known. The degenerations of the short and commissural tracts near the lesion are obvious, but not extensive. The degenerations in the long tracts other than those described are difficult to estimate, and particularly difficult to translate into functional terms because the fascicles are composed of a mixture of fibers, some of which are ascending and others descending. The posterior columns show, besides the extensive degeneration above the plane of lesion, also small (in cross-sections comma-shaped) tracts of degeneration below the plane of lesion. The fibers concerned in this descending degeneration are the descending branches of the dorsal root fibers.

Unilateral Lesions of the Spinal Cord.

Stab wounds occasionally produce hemisection of the spinal cord, upon which follows the symptom complex known as Brown-Séquard's paralysis. The anatomical basis of this symptom complex is in part obscure. Paralysis on the side of the lesion is due to section of the direct pyramidal tract. Anesthesia on the side opposite to the lesion is supposed to be due to the section of sensory fibers which decussate immediately after entrance into the cord. But the anesthesia is incomplete, as the muscular sense is intact; accordingly the fibers corresponding with muscle sense are supposed to decussate higher up. Complex but quite definite symptom groups are produced by lesions at various levels. It is impossible, as it would be unwise, to learn these complexes by rote. Only familiarity with the anatomy of the cord and results of experimental work permits diagnosis.

SYSTEM DISEASES.

The conditions sketched under secondary degeneration are the outcome of known destructive injuries. Roughly similar degenerations, in point of extent, are produced in various unknown ways. The best defined of these degenerations occur in tabes, in progressive muscular atrophy and amyotrophic lateral sclerosis, and anterior poliomyelitis. At present, however, anterior poliomyelitis may be ranged perhaps better with the results of bacterial inflammation.

Together with these conditions may be considered the combined system disease and multiple sclerosis.

Tabes Dorsalis.

A small percentage of syphilitic subjects five to fifteen years after infection, and a number of other subjects in whom syphilis cannot be proved, are attacked by a disease which early exhibits loss of knee-jerks, Argyll-Robertson pupil (accommodating for distance, but failing to respond to light), lancinating pains in various parts, analgesia usually of the lower extremities, and, perhaps, Romberg's symptom (swaying with closed eyes). Other phenomena are added later and give tabes its other name, locomotor ataxia. The disorder of movement is due, not to weakness, but to incoördination, and usually affects the lower extremities first. The most frequent disease of the cranial nerves is paralysis of the oscular muscles (the only true motor symptom of tabes). The optic nerves often undergo progressive atrophy. Characteristic are disturbances of the joints and bones, malum perforans (perforating ulcer, as a rule, of the sole of the foot), spontaneous gangrene, and other disorders all referable to destruction of the trophic apparatus of the spinal cord. The degenerations of tabes progressively attack various regions of the spinal cord. The initial sclerosis may be quite invisible to the naked eye, as the change is quite narrowly confined to the region of the dorsal root zones of the middle or lower lumbar segments of the cord. The disease is not easily recognized from the gross cord till later stages, in which a flattening and narrowing of the posterior columns of many lumbar and thoracic segments is observed. But in the middle stages it is still possible to make out an increase of consistence and a slight graying-out of the posterior columns examined in cross-section. The stage of the disease is more surely determined by microscopic examination of various cord levels. The older the process locally, the more marked the atrophy and the corresponding gliosis and the smaller the area of degeneration as seen in cross-section. The more advanced the disease, as a whole, the more entering dorsal root fibers are affected, and the wider will be the ascending tracts of degeneration in the posterior columns. It is in this disease that the prettiest demonstrations are afforded of the relationship between the columns of Goll and of Burdach and the lower and higher dorsal root systems respectively. Thus in an early case of tabes dorsalis an examination of serial sections from below upward exhibits the ascending prism of degenerated fibers slowly translocated inward, to form the column of Goll, through the accession of fresh undegenerated fibers from higher nerve roots. In the rare cases of cervical tabes the relationship is reversed. In cervical segments from a case of tabes cervicalis, it is the fibers of the column of Burdach which are degenerate; whereas the fiber system of the column of Goll, derived from the intact roots and ganglia of the lower dorsal and lumbar regions, remains unaffected. However, in the majority of cases of tabes dorsalis, seen at autopsy, the changes are already spread over many segments, and there may usually be seen gross thinning out of the dorsal columns.

Progressive Muscular Atrophy.

Persons in middle life may become subject to a slowly developing disease, which starts with a flattening of the ball of the thumb and a deepening of the interosseous spaces in the hand. Fibrillary twitchings and gradual atrophy ensue. The atrophy overtakes various muscles of the arm and shoulder, not by continuity, but by springing from one group irregularly to another group of muscles. In the course of several years most of the arm, shoulder, and back muscles are atrophied, and the muscle groups which are spared undertake, as well as possible, the functions of the atrophic muscles. The so-called "living skeletons" die of intercurrent disease or are destroyed by an advance of the atrophy upon the respiratory and other muscles controlled from the bulb.

The spinal cord, at appropriate levels, shows a variety of degenerations of which the most constant is atrophy of the anterior horn cells.

Amyotrophic Lateral Sclerosis.

Men of thirty to forty years sometimes become subject to a disease consisting in paresis and contracture of the arms or of all the extremities, in which the muscles undergo atrophy. The disease is apt, later in its subacute course of eighteen months to two years, to involve also the muscles of the tongue, the face, and the pharynx. Death is likely to ensue when the pneumogastric nerve becomes affected.

Nothing is known of the cause of this disease, but the findings in the nervous system are striking. The cells of the anterior horns in the cord at levels corresponding with the muscular atrophies are reduced in number and size, perhaps overpigmented. Especially the large motor cells are affected. The cells of Clarke's column remain intact. The nerve fibers of the anterior horns, the anterior root, and of the direct and crossed pyramidal tracts have disappeared. The area of the crossed pyramidal tract affected is, as a rule, larger than the similar area brought about by secondary degeneration. That the disease is progressive is shown by the occurrence of fresh fatty changes in other parts of the cord alongside the typical sclerotic lesions.

Analogous lesions to these are found, in the glosso-labio-pharyngeal cases, in the cells of the hypoglossal, facial, motor trigeminal, and finally the pneumogastric nuclei, together with a sclerosis of the anterior pyramids. Essential changes are rarely found above the level of the pons. Thus, at a given level, both the whole of the spinomuscular motor path and the lower portion of the corresponding corticospinal motor path are affected.

ACUTE ANTERIOR POLIOMYELITIS.

Acute anterior poliomyelitis is a disease characteristically found in children. Its healed results are seen in cases of infantile spinal palsy. The process, when caught early, is found to be a true inflammation of the region of the anterior horns, preferably of the cervical and lumbar enlargements of the cord.

Too few cases have been examined early to warrant saying which organism is the most frequent cause. Cases examined at various stages later in the disease show, first, fatty degeneration (Marchi), later, scleroses demonstrable by Weigert's myelin sheath method. Finally a stationary stage is reached in which a certain amount of atrophy in one or both anterior horns can be grossly demonstrated, and a reduction in number of motor cells with gliosis can be made out microscopically.

COMBINED SYSTEM DISEASE.

A peculiar though varying set of symptoms sometimes occurs in pernicious anemia. The same symptoms and the same findings certainly also occur in cases which are not pernicious anemia. The beginnings of the disease have never been microscopically observed. The spinal cord simulates a combination of tabes with degeneration of the pyramidal tracts: thus the posterior columns and the direct cerebellar tract are degenerated, as well as the crossed and sometimes the direct pyramidal tracts.

The symptoms cannot be a mere combination of tabetic and spastic paretic phenomena, for some of these are contradictory. As a fact, according to the distribution and intensity of the lesion, two types of symptoms are found. In the first place, the motor weakness with increase of tonus (spastic paralysis) may be combined with various tabetic symptoms, such as ataxia, lancinating pains, Argyll-Robertson pupil. Or, in the second place, the picture may be predominantly that of tabes, with a motor weakness not found in tabes.

A disease exhibiting somewhat the same distribution of degeneration in the cord (degeneration of Goll's and Burdach's tracts, of Clarke's gray column and the direct cerebellar tract, together with degeneration of the crossed pyramidal tract), besides in certain cases atrophy of the cerebellum, is known as *hereditary ataxia* (Friedreich's disease).

MULTIPLE DISSEMINATED SCLEROSIS.

Young adults, after acute infectious diseases and metal poisoning, or apparently spontaneously, sometimes develop a striking clinical picture: weakness and rigidity of legs, spastic paretic gait with "cerebellar" reeling, tremors attending and increasing with voluntary movements ("intention tremor"), nystagmus (especially on looking sidewise), partial optic atrophy, "scanning" or "syllabic" speech, paroxysmal involuntary laughter, and weakening of intelligence.

To account for these phenomena the central nervous system shows multiple areas of degeneration, which in Weigert myelin sheath preparations are quite sharply demarkated through absence of myelin from surrounding areas. In glia preparations the areas are by no means so sharply marked. Many axis cylinders are preserved in the midst of the fibrillary overgrowth of glia.

SYRINGOMYELIA.

Persons in middle life may notice vesicles on the skin of the hands which fail to heal well. Slight wounds become easily produced. The small muscles of the hand atrophy; the interosseous spaces deepen; fibrillary tremors, "claw hand," and the picture of progressive muscular atrophy develop. The physician may be the first to detect a peculiar disorder of sensibility; whereas the sensations of touch, pressure, and position are intact, the sensations of pain and temperature are lost or decreased over wide areas (*dissociation of symptoms*).

The clinical picture is typical only because of the usual site of the fusiform glia-lined cavity, asymmetrically set, as a rule, a little posteriorly in the central gray of the cervical cord. A condition histologically exactly similar but of different site would produce a quite different picture. The clinical picture is as characteristic and definite as many of those in the system diseases, but the process is not a tract disease.

GENERAL PARESIS.

The brains of some subjects exhibit a characteristic set of changes: the pia mater is thickened almost diffusely and may be edematous; the convolutions are narrowed over limited but wide areas, and the sulci are flaring; small bits of the cortical substance may cling to the pia on peeling; on section the minute cortical vessels stand out prominently. Notwithstanding the absence of arteriosclerosis, there is likely to be a moderate internal hydrocephalus and marked granular ependymitis. Microscopically the cortical vessels attract attention from the infiltration of their sheaths with lymphoid and many plasma cells. The neuroglia shows many phases of overgrowth. The swelling of the neuroglia cell bodies may be determined in regions where defined nerve cell changes are still absent. In many areas the nerve cells exhibit changes of many grades up to replacement. Their regular radial arrangement in the cortex is disturbed. The regular rows of neuroglia cells in the white matter are thrown into disorder by the loss of medullated fibers and the irregular contraction of the intercellular substance.

If the records of the subject be examined, it may be found that syphilis had occurred many (five to twenty) years before. The symptoms which have led to death had begun insidiously two or three years before: a change of character (*e.g.*, from grave to gay or contrariwise) with moral and intellectual impairment and loss of memory. The disease then progresses to graver impairment in which speech disturbance and paralytic attacks are prominent. The pupils show the Argyll-Robertson sign as a rule.

GENERAL DISTRIBUTION OF MUSCULAR PARALYSES AND ATROPHIES.

The distribution of muscular paralyses and atrophies varies with the site of the lesion which produces them. This distribution follows one of four types:

I. Peripheral.
II. Radicular.
III. Medullary and spinal.
IV. Cerebral.

Paralyses and atrophies of peripheral origin are grouped according to the anatomical distribution of the nerves or plexuses involved by lesion. Trauma or pressure may produce effects strictly limited to certain muscle groups. Infectious or toxic injuries to the peripheral nerves produce effects, as a rule, more marked distally (as in the hand or foot).

The radicular paralyses and atrophies ensue upon lesion of the anterior roots and of the trunks of origin in the great plexuses. Almost all the muscles are innervated by fibers in at least two anterior roots. The trunks of origin of the cervical, brachial, lumbar, and sacral plexuses already contain an admixture of sensory with the motor fibers: the paralyses and atrophies of radicular origin are therefore attended by sensory disorders of similar strict localization.

With respect to the myelopathic paralyses and atrophies, which ensue upon lesion of the pyramidal tracts and of the anterior horns respectively, the weight of evidence at present indicates that they follow in general the radicular distribution. Other types of distribution are logically possible and have at various times been assumed, such as a limited distribution with a given nucleus for a given muscle group, or a segmentary (metameric) distribution, or a more diffuse distribution of non-radicular type. The radicular type of distribution is demonstrated well at times in cases of syringomyelia, hematomyelia, and acute anterior poliomyelitis, but may be less distinctly seen in diseases of a more diffuse extent, as in amyotrophic lateral sclerosis, wherein the paralysis and atrophy follow a double lesion of pyramidal tracts and anterior horns.

The distribution of paralyses of cortical origin is rarely as sharply limited as the distribution of muscular contractions excited electrically at the cortex. The lesions are almost without exception too extensive for such focal results; and results less gross than a hemiplegia or a monoplegia are rare in cortical lesions, and still rarer in subcortical or capsular lesions. The muscle groups which subserve the more specialized functions are more apt to be incurably involved in these lesions than the muscles of lower function.

V. THE NEURONE THEORY.

Waldeyer, 1891, offered the following definition of the nervous system: The nervous system is a collection of units which are anatomically and developmentally distinct. Each unit or neurone is composed of three parts, namely, of a nerve cell, a nerve fiber, and a terminal arborization. Conduction proceeds in some neurones from cell to arborization, but in other neurones from arborization to cell. Thus motor impulses are conveyed from cell to arborization, but sensory impulses, on the other hand, run one way in some instances, but in other instances go contrariwise (note, for example, the directions of impulse in the processes of the cells of the dorsal root ganglia).

Waldeyer's definition took its rise from the data of the silver impregnation methods of Golgi, and particularly from Ramón y Cajal's demonstration that the nerve cells of embryos and fetuses throw out processes which all end blindly. However, it has never been so clear that the nerve cells of the adult invariably remain anatomically distinct. Edinger and others have held that although there must remain a doubt whether the processes are continuous or only contiguous, nevertheless the neurone must be maintained as a biologically independent unit.

The neurone theory has thus undergone various changes since its first exposition. The most frequent insistence is made upon the trophic nature of its function. An explanation seems demanded for the data of Wallerian degeneration and the invariable results of the method of Gudden. Thus, if destruction of a given gray center or section of a given nerve bundle constantly produces retrograde changes in certain remote circumscribed foci and the connecting paths, it is certainly possible to regard the cells involved as neurones, as units having a functional value and unity, whose anatomical nature may be left out of account.

Many of the tract diseases sketched above are neatly interpretable in terms of the neurone theory. Thus, the pyramidal tract may be considered to be a bundle of fibers belonging to the *corticospinal neurone system.* The corticospinal neurone system may be said to come into relation in the anterior horns with a peripheral or *spinomuscular neurone system.* Further, to take up the sensory half of the loop made by the projection system, the apparatus connecting sensory end organs with higher centers, which consists for the spinal cord of the dorsal root ganglia, the sensory peripheral nerves and the columns of Goll and Burdach may be termed the *gangliospinal neurone system.* The central (intraspinal) tracts of the gangliospinal neurone system come into relation with new ascending neurone systems in the medulla (*bulbocentral neurone systems*), of which we suppose, on account of the rapid playing out of degeneration tracts at higher levels, there is an end-to-end series. Moreover the direct cerebellar tract, which becomes degenerate on section of the thoracic cord, may, in conjunction with the cells of Clarke's column from which it takes its rise, be regarded as a fresh neurone system, a *spinocerebellar neurone system.*

In a certain series of diseases (secondary degenerations, tabes dorsalis, anterior poliomyelitis, and so on) these neurone systems undergo changes as units. In some of the diseases our attention has been directed by this consideration to look for changes in the gray centers which might otherwise have been overlooked. It would be oversanguine to assume that actual progress in making clear the facts has been accomplished by the neurone hypothesis. In so far as it restates facts and discoveries made in most cases without its use, the hypothesis may be assigned a limited value. But the true cause of the so-called primary degeneration remains remote from us. It remains mysterious why the intraspinal portion of the gangliospinal neurone system is chiefly affected in tabes, why in amyotrophic lateral sclerosis and in progressive muscular atrophy (if they are separate diseases) the spinomuscular neurone and a portion of the corticospinal neurone are affected, and why the process in anterior poliomyelitis should sometimes be confined to the spinomuscular neurone system and sometimes involve also the direct cerebellar tract. In the latter case it is probable that the simple explanation suffices that in some cases the acute inflammatory process is at the outset more extensive than in other cases.

The neurone terminology is now widespread and is harmless, so long as the tendency does not grow of supposing certain diseases to grow spontaneously out of the unitary structure of the neurone. The neurone theory is an interesting restatement which explains nothing as to the nature of diseases peculiar to the nervous system, but may sometimes give hints as to their extent.

Extracted from The American Journal of the Medical Sciences, October, 1904.

III

A CASE OF GLIOMA IN THE SELLA TURCICA.[1]

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(From the Pathological Laboratory of the Boston City Hospital.)

Following is a case of new-growth in the pituitary region peculiar in producing an intercellular substance which stains like neuroglia. The tumor grew in all directions and notably forward and downward, with partial destruction of the gland and perforation into the sphenoidal sinus. Death occurred six years after onset of symptoms. There were symptoms of heightened intracranial tension, impairment of vision, an unusual kind of ("ear-to-ear") headache, and rhinitis. There was no acromegaly.

Clinical History. Mrs. ——, aged forty-eight years, family history good, previous health good.

History of present illness: Early in 1897 patient noticed slight impairment of vision. In July, 1898, the visual defect grew worse, and slight headaches developed. Dr. Knapp then examined her eyes, with results as follows: Right eye counts fingers eccentrically at 30°; left eye 20/40, with + 1 D. glass 20/30; ophthalmoscope shows right optic atrophy; no other intraocular disease. A second examination by Knapp in April, 1899, showed that right eye could see only movements of the hands; left eye with + 1 D. glass 20/30; there was complete bilateral temporal hemianopsia, and the nasal field of right eye was much contracted, extending only 20 degrees toward the nasal side.

In August, 1899, there occurred an attack of coma ushered in by violent headache and nausea. With slight remissions, the attack lasted several days. There were no convulsions. Following this illness mercury inunction and potassium iodide were used, and the patient regained the degree of health possessed before the attack. During the winter (1899-1900) headaches became more frequent; they were often frontal in location, but frequently seemed to transfix the head, passing from ear to ear. Rhinitis developed, and with every exacerbation of the nasal congestion the headache became worse. There was some unsteadiness of gait.

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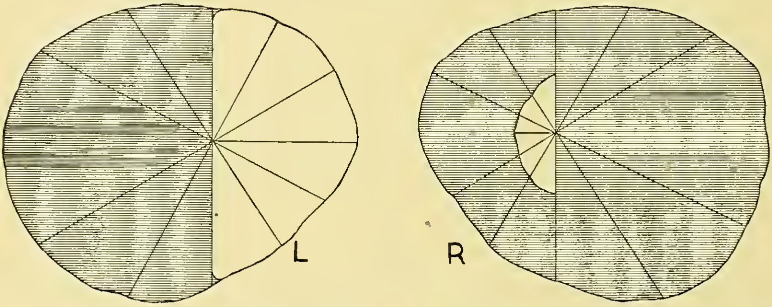
[1] Presented at the Fourth Annual Meeting of the American Association of Pathologists and Bacteriologists, New York City, April 2, 1904.

In August, 1900, a briefer attack of coma occurred similar to that of 1899. In January, 1901, a third attack. One of us (F. H. H.) saw the patient in this attack. There was absolute coma, flushed face, slow, full pulse, fever, strabismus. There was and had been no sign of nephritis, neither was there paralysis at any time (except the ophthalmoplegia). There were no convulsions. The attack lasted about one week, during three days of which the patient was comatose.

A fair measure of health was regained after this attack, and maintained for two years. During this time the patient was fairly active, walking on the street daily, though with unsteady gait. There were occasional headaches. On two or three occasions there were transient seizures of violent headache and nausea, but without coma. The visual defect progressed until the right eye was totally blind and vision very defective in left.

Fig. 1.



Visual fields, showing bilateral temporal hemianopsia (from the notes of Dr. Herman Knapp two years after the onset of symptoms).

In April, 1903, a final attack similar to former ones occurred and terminated in death.

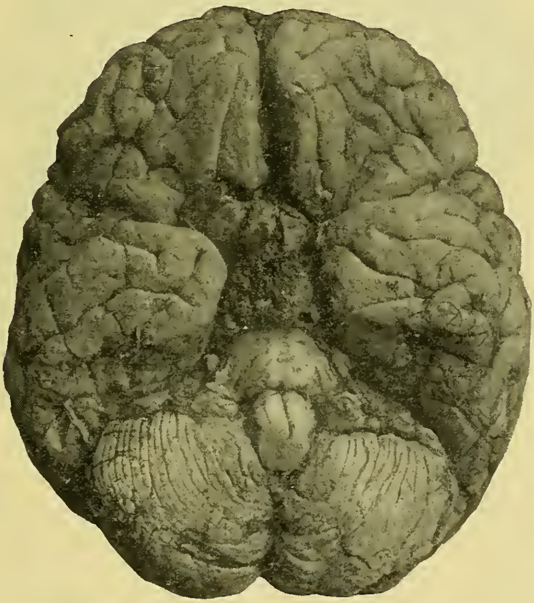
(Dr. E. E. Mather, of Williamstown, physician to the patient, has kindly given us many of the clinical data. Notes of the ophthalmic findings have been kindly furnished by Dr. Hermann Knapp, of New York. A part of the neurological account is due to Dr. M. Allen Starr, of New York, who saw the patient at various times during her disease.)

Clinical Summary. Symptoms at intervals during six years. Progressive impairment of vision. Frontal and ear-to-ear headache, more severe in attacks of rhinitis. Various seizures with headache and nausea. Attacks of coma forty-four, thirty-two, and twenty-seven months before death. Death in a fourth attack.

Gross Findings. *Necropsy.* Performed twenty hours postmortem. The cranium only was opened.

Body well nourished. Physiognomy normal. Calvarium of normal thickness. Pial vessels much engorged. No increase of arachnoid fluid. On raising frontal lobes a mass is seen in the neighborhood of optic chiasm, firmly adherent in places to sella turcica. Floor of sella thinned and broken through in places, opening into the sphenoidal sinuses, which contain pus. From below a conspicuous dark-brown mass is seen to occupy the interpeduncular space and to extend from the pons forward beyond the position of the optic chiasm. (Fig. 2.) The tumor hides all parts of the visual path except the extremity of the divided left optic nerve. Projecting from the tumor anteriorly, dorsally, and laterally into the right frontal lobe is a cyst of hazelnut-size containing a clear blood-tinged fluid. A mesial section of the brain (Fig. 3) shows that the tumor lies anterior to the corpora albicantia, occupying the position of the pituitary body. The floor of the third ventricle is stretched over the dorsal surface of the tumor, and is melted down in part, so that the tumor projects into the third ventricle, encroaching to some extent upon the anterior portion of cavity. The tumor projects dorsally through cerebral substance into the lateral ventricle. The lateral ventricles are somewhat dilated.

FIG. 2.

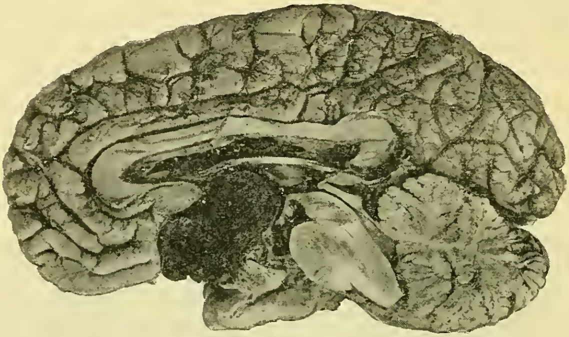


Ventral aspect of brain, showing tumor in interpeduncular space.

The chiasm and the right optic nerve are totally destroyed. The tumor itself is thinly encapsulated and shells out easily from its bed of cerebral substance, and is of a spongy consistence anteriorly, more compact posteriorly. The spaces of the spongy tissue are filled with cruor clots.

Summary of Gross Findings. Single, compact, in places spongy or hemorrhagic tumor, filling interpeduncular space, producing atrophy of floor of sella turcica, encroaching upon lateral and third ventricles, and effecting atrophy and complete destruction of optic chiasm and right optic nerve, with partial destruction of optic tracts.

FIG. 3.



Mesial aspect of brain.

FINER ANATOMY. Endeavor was made to get at the duration of the process by tracing out roughly the degenerations in the optic apparatus. More evidence was obtained from the tissues of the tumor itself upon the crucial point of the relative age of its different parts.

The microscopic findings follow:

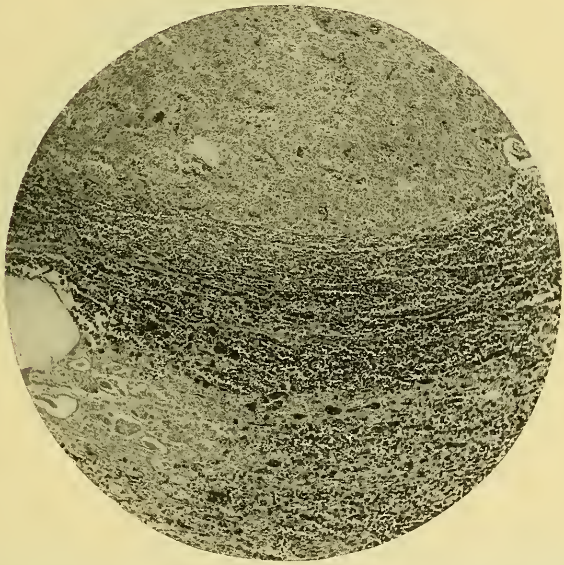
1. The cortex in many places, though not everywhere, exhibits slight neuroglia changes, consisting in a moderate increase of the large neuroglia cells of the subpial layer and an increase (or increased staining capacity) in the fibrillæ in the outermost lamina. We should like to interpret these changes as a response to the universal pressure and consequent flattening which attend new-growth or other swelling in intracranial tissues. Sections from the orbital cortex adjacent to the tumor show the thickest fibrillæ, which are arranged as a rule tangentially. In general there are more fibrillæ in the sulci than over the tops of the gyri. There is some evidence for maintaining that there are more fibrillæ (without notable increase of cells of origin) opposite the vessels and especially opposite the larger arteries (compare fibrous increase in supra-arterial epicardial nodules). The method of demonstration here used was the phosphotungstic-acid-hæmatein method after formalin fixation and mordanting with picric acid and ammonium bichromate (Mallory).

2. Work with the Nissl method (paraffin sections of formalin-fixed material) was negative or unsatisfactory. The adventitial

spaces about the smaller vessels are free from exudative cells. Many of the isolated glia cells and some of the satellite cells show numerous coarse grayish-green pigment granules in limited masses serving very well to mark out the glia cell bodies which are not otherwise in evidence. Similar appearances are sometimes shown in Zenker-fixed material of various origin and without other lesion. Many of the nerve cells are moderately pigmented. The nerve-cell picture is unsatisfactory. Many of the nuclei are swollen; some show foldings of the nuclear membrane. The cell layers are demonstrable. The medullary glia shows an orderly arrangement of nuclei.

3. Unmistakable early degeneration is demonstrable by the Marchi method in the left optic nerve (central bundles show the most distinct blackening), in the left lateral geniculate body (dense bundles of degenerate fibres intercalated with normal bundles), in the left anterior quadrigeminal body (stratum zonale shows marked change, many of the sagittal fibres of the nucleus are blackened), and in the lateral geniculate and anterior quadrigeminal bodies on the right (diffuse changes).

FIG. 4.

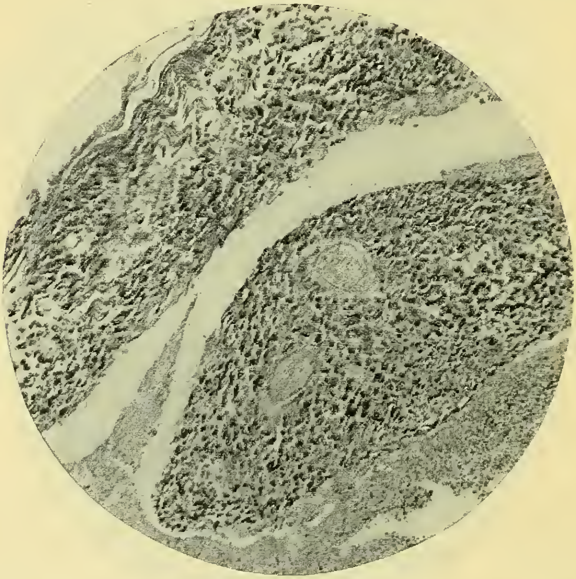


Section showing strands of gland substance of anterior lobe of hypophysis compressed by the tumor. The gland contains numerous masses of colloid. The cytoplasm of the chromophile cells of the gland stains deeply with phosphotungstic-acid-hæmatein. (Mallory.)

Longitudinal sections of the left optic nerve stained by the Weigert method for myelin show almost total loss of staining capacity except in a central core (probably attacked last, as shown by the Marchi method). The lateral geniculate bodies and the anterior quadrigeminal bodies stain well by Weigert; probably all the fibres of the stratum zonale and most of the fibres of the nucleus retain the stain. A small area of undoubted degeneration of some standing was made out by the Weigert method in the left pulvinar; but this was not further traced.

4. Microscopic examination of various portions of the tumor showed, first, some anterior pituitary substance; second, neoplastic tissue adjacent to and compressing the glandular substance. (Fig. 4.) The new formation showed an almost homogeneous structure except in amount of fibrillary intercellular substance. (Fig. 5.)

FIG. 5.

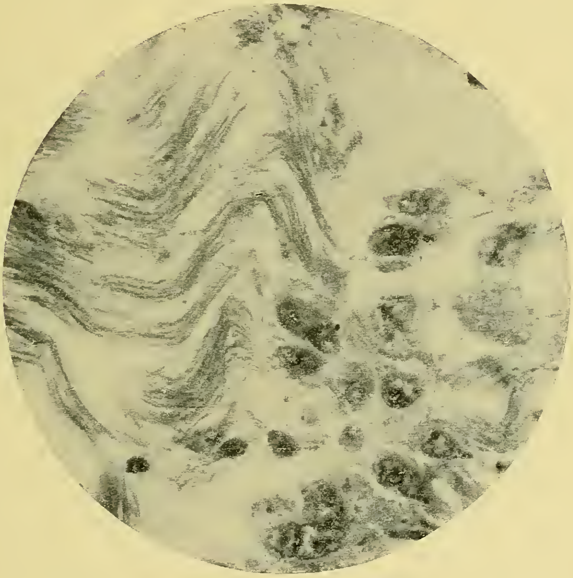


Low power view of tumor, showing trabeculæ of cells separated by a space containing blood and coagulated serum. The lower band of cells shows a striate or wavy structure due to the included fibrillæ. Section stained with Mallory's phosphotungstic-acid-hæmatein (formol fixation, mordanting with picric acid and ammonium bichromate).

The mass contains numerous well-developed vessels besides numerous thin-walled vessels, many of which have ruptured to form fairly wide lacunæ of blood. The cells are in many places so grouped about the vessels as to suggest the appearance of certain sarcomata of vascular origin.

Owing to poor fixation or on some other ground it seemed impossible to prove the tumor a sarcoma by demonstrating an intercellular substance responding to the aniline-blue stain (Mallory). Attention was therefore drawn to a very few scattered fibrillæ taking the acid fuchsin in the aniline-blue method. With a view to making out the nature of these fibrillæ, pieces of the mass from a part adjacent to the bone were mordanted by the picric acid and ammonium bichromate process and stained by phosphotungstic acid hæmatein. By this method numerous bundles of parallel fibrillæ standing in the characteristic cage-like relation to the cells are demonstrable in the inferior peripheral layer of the tumor. (Fig. 6.) These fibrillæ are in places shown adjacent to the connective tissue which invests the older vessels, and can here be shown to differ in form as well as in staining reaction from the connective-tissue fibrillæ. The fibrillæ are demonstrable in fewer and fewer numbers as one advances toward the core of the tumor; but, whether they are not yet developed or for some reason do not stain, it is not possible to say. The fibrillæ of the peripheral zone can be demonstrated by phosphotungstic acid hæmatein alone (without the preliminary mordanting process) and also by Weigert's method for neuroglia fibrillæ.

FIG 6.



High power view of tumor, showing bands of smooth, fairly coarse, parallel fibrillæ, bent about characteristically at acute angles. Field and staining method same as in Fig. 5.

The cells are rather large and of an oval or irregularly polygonal shape. The cells of the non-fibrillary core of the mass never show processes and rarely reentrant angles; but the cells about which the fibrillæ are disposed are often supplied with numerous processes to which fibrillæ may sometimes be seen in close apposition. But few mitoses are demonstrable. There are, however, numerous cells with several nuclei, as a rule centrally set. No ependymal dots have been as yet discovered in the tumor.

(The microscopic examination was carried out in the pathological laboratory of the Boston City Hospital during the service of Dr. F. B. Mallory, to whom we are indebted for supervision of the work.)

REMARKS. The report may be summed up as follows:

A new-growth at the base of the cranium gives rise to somewhat characteristic symptoms ending in death after six years. The tumor has gradually filled the interpeduncular space, giving rise in the lower optic apparatus to certain degenerations, a part of which are complete, a part still in process. The brain at large shows little reaction save a subpial gliosis, perhaps incidental to the heightened intracranial tension.

The nature of the growth is in question. The oldest portion of the tumor (judging by the development of the fibrillæ) is in the locus of the posterior lobe of the pituitary gland, which lobe normally contains neuroglia cells developing fibrillæ. The rest of the tumor contains few demonstrable fibrillæ, and could scarcely be differentiated from a sarcoma. It is probably justifiable to classify the case as one of glioma developing in the posterior lobe of the pituitary body. We are not acquainted with previously reported cases of such tumors. Definite proof of the existence of this tumor type can only be brought when some fortunate case shall be dissected showing such a growth in the midst of, or patently growing from, an otherwise normal pituitary body.

Extracted from the American Journal of the Medical Sciences, March, 1905

A STUDY OF ACUTE HEMORRHAGIC ENCEPHALITIS (STAPHYLOCOCCUS PYOGENES AUREUS).

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(From the Pathological Laboratory of the Boston City Hospital.)

Following is a study of encephalitis in man, due to the staphylococcus pyogenes aureus. Parallel lesions have been studied in guinea-pigs, with a view to establishing the time limits and order of the acute inflammatory changes.

A text for the present work was afforded by some points of a case, previously reported at length,[1] of cortical hemorrhages ensuing upon subinfection with the staphylococcus pyogenes aureus during convalescence from scarlet fever in a boy aged five years. An abstract of this case follows:

Case I.—*Abstract.* About five weeks after onset of scarlet fever, convalescence was interrupted by cerebral symptoms, and death occurred two weeks later (seven weeks after admission). The contractions and sensory symptoms began in the right leg and advanced during four days to affect the whole right side, including the face. The contractions were sharply defined (at one time alternating regularly with relaxations at intervals of about ten seconds) and limited in duration (a few minutes). Paralysis of the affected limbs ensued. During the last week the child was in the main unconscious (masking symptoms on left side).

At autopsy the organs and tissues showed little gross evidence of lesion, beyond desquamation of skin and fresh and pigmented hemorrhagic lesions in the cortex of both parietal lobes, with œdema of overlying pia mater.

Microscopic study showed an early bronchopneumonia and septicæmia (staphylococcus pyogenes aureus) and a purulent inflammation of foci in the parietal pia mater and overlying arachnoidal villi. Besides large areas of hemorrhage in the cortex, there was extensive development of cells phagocytic for polynuclear leukocytes, blood corpuscles, and fatty detritus. These phagocytes lay in meshes of the pia mater and in the adventitia of the short arteries of the cortical system. The phagocytosis was accompanied by solution and fatty changes of adjacent nerve tissues. Fatty changes in associated motor systems and early changes (axonal degeneration of anterior horn cells by Nissl method) in the lower motor systems.

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[1] E. E. Southard and F. R. Sims. A Case of Cortical Hemorrhages following Scarlet Fever, Journal of the American Medical Association, September 17, 1904.

The interpretation of Case I. is not wholly clear. Suspicion, however, attaches to the staphylococcus pyogenes aureus and its toxins for the production of some of the cerebral lesions. A study has therefore been made of further accessible cases of septicæmia and encephalitis associated with the staphylococcus aureus to find what aspects are held in common. Abstracts of these cases follow:

Case II.—*Clinical History.* A. B., a girl aged twelve years, was admitted to Dr. G. C. Sears' service at the Boston City Hospital January 7, 1901. On entrance she was wildly delirious. Her head was retracted, and there was spasm of the posterior cervical muscles, with inability to flex the head. The pupils were widely dilated and failed to react to light. Both tonsils were enlarged, and the tongue bore a heavy white fur. There was a loud, rough, systolic murmur audible throughout the heart area, but at its maximum in the second left intercostal space and over the apex. The murmur was transmitted into the vessels of the neck, the axilla, and the back. There were a few moist rales at bases of lungs behind. The abdomen was everywhere tympanitic, and there was slight voluntary spasm of the walls. The reflexes were normal. Over outer aspect of right ankle, extending from a point 18 cm. above external malleolus to the heel, was an erythematous swelling, acutely tender and painful on passive motion. Below malleolus were three small pustules with incised (surgical) wound.

The origin of this condition is unknown. Four days before she had the first symptoms of her illness, chilly feelings and frontal headache. The next day small black spots were noted on the right foot, and an incision was made. The next day (third of the attack) she vomited after meals. Then gradually supervened the condition at entrance as above described.

The girl was fairly well developed, but poorly nourished. She is said to have had rheumatic fever at six years of age, scarlet fever at nine, measles at ten, and was just recovered (five weeks) from diphtheria. It is not possible to say what importance attaches to any of these events.

The day after entrance fresh inflammatory areas developed over the head of the fifth metatarsal bone of the left foot and the inner aspect of the left wrist. The leukocytes were but 10,000 per c.mm. The patient immediately vomited the food administered by nasal catheter.

The evening of the third day after entrance the patient died without notable change of condition.

Clinical Summary. Girl, aged twelve years, just recovered from diphtheria, with history of rheumatic fever, scarlet fever, and measles. Onset of attack, chilly feelings, and frontal headache, with development of purulent hemorrhagic areas on right foot, and vomiting two days later. Four days after onset, admitted in delirium, with suppurating wound of heel and heart murmur. Retraction of head. Dilatation of pupils, which failed to react to light. Development of fresh superficial inflammatory areas. Death eight days after onset of symptoms.

The autopsy was performed by one of us (E. E. S.) January 10, 1901. Following are the findings in the head:

Brain, weight 1200 gms. Dura tense, convolutions somewhat flattened. Density of brain about normal except right occipital lobe, which is semifluctuant. On section there is found near the apex of this lobe a rather firm, irregular mass of clotted blood, 3 cm. in greatest diameter. It reaches to within 1 cm. of surfaces of brain, but does not show externally. Around the clot is more or less fluid blood. The adjoining brain tissue for some distance is stained reddish-brown and is of soft consistence. The hemorrhage has extended into the right lateral ventricle, where fluid blood is present. A little is present also in the left ventricle.

Anatomical Summary. Wound of heel, with purulent infiltration of adjoining tissues; infective thrombus left ventricle wall; multiple abscesses of heart wall, kidney, adrenal, liver, spleen, intestines; diffuse small hemorrhages of lungs, kidney, epicardium; hemorrhages and softening of right occipital lobe; fatty degeneration of myocardium and skeletal muscles; chronic endocarditis (mitral); chronic adhesive pericarditis; chronic pleuritis of left lung and right apex.

Microscopic Findings. Cultures from the organs showed a septicæmia due to the staphylococcus pyogenes aureus. The growths were pure except from the kidney, which showed, besides the staphylococcus, an organism of the colon-typhoid group.

The histological examination of the various organs confirmed the diagnoses from gross findings. The lung shows small hemorrhages, chiefly without leukocyte reaction. The marrow of the femur is very cellular, containing numerous leukocytes of the mononuclear series, but very rare polynuclear leukocytes.

Special study of tissues from the brain was made by a variety of methods.

The subcortical lesion in the occipital lobe shows wide sheets of clear, well-preserved blood, with occasional polynuclear leukocytes and several foci of staphylococci, both free and within cells. The hemorrhage penetrates the cortical tissue along lines of least resistance between the radiating bundles of nerve fibres. Occasionally large vessels from the cortical system run free through the blood, with the adventitial meshes dilated with polynuclear leukocytes and occasionally embraced by areas of coarse fibrin. Near the vessels there occur purulent areas, with fatty changes, pigment, fat-containing and pigment-containing phagocytes, and without notable evidence of repair. Adjacent to the hemorrhagic areas the myelin, as a rule, stains perfectly; but a few fibres are represented in Marchi sections by linear collections of black dots. The nerve cells occasionally show changes, as a rule attributable to swelling or shrinkage due to œdema. These changes are scarcely more marked near the hemorrhage than remote from it.

Case III.—*Clinical History.* H. H., a man, aged twenty-two years, was admitted to Dr. G. B. Shattuck's service at the Boston City Hospital, December 5, 1903. On entrance he was unconscious and restless, with flushed cheeks and equal, contracted pupils, reacting sluggishly to light. There was slight rigidity and retraction of neck. The abdomen was slightly retracted and rigid, with tenderness over pubes. The legs were flexed and rigid. The hands and feet were blue, and there were irregular hemorrhagic areas about thumbs and over outer surfaces of both feet and the toes. The knee-jerks were normal. Kernig's sign and Babinski's sign were absent.

The attack had begun the day before, with increase in frequency of micturition and general discomfort. The physician, Dr. C. L. Knight, had forthwith suspected cystitis, as he had had the patient under treatment for some time for urethritis. In the afternoon of the day before admission the patient complained of severe pains in various parts of the body, especially the thumb and ankle. Nausea, vomiting, and delirium followed.

The day after admission (the third day of the symptoms) the patient died, without marked change of condition. The pulse, at first of moderate rate, later became rapid, small, and easily compressible. Cyanosis increased. The chest became filled with moist rales. The ecchymoses of the extremities slowly increased in extent. The pupils became widely dilated and still reacted sluggishly to light. The reflexes remained as before; there was some question whether Babinski's sign was present.

Clinical Summary. Man, aged twenty-two years, with history of treatment for urethritis. Onset of attack with increased frequency in micturition and malaise. Later in the day various focal pains, nausea, vomiting, delirium; cyanosis; ecchymoses on thumb, ankles, and toes. Pupils at first contracted, before death dilated. Death on the third day.

Autopsy Findings. The autopsy was performed by Dr. R. L. Thompson and one of us (E. E. S.) December 7, 1903. The findings in the head were:

Head. Hair dark and fairly thick. Scalp normal. Cranium of the usual thickness. Dura externally smooth and tense. Sinuses contain fluid blood with cruor clot. Pia over left hemisphere almost dry, and tightly stretched over flattened convolutions and effaced sulci. There are a number of irregularly distributed ecchymoses, varying in diameter from a pin's head to 0.5 cm. or more, rarely 0.75 cm., either within meshes of pia at lips of sulci or shining through from cortical substance. In the region of the left supra-angular gyrus are two well-defined ecchymoses, with irregular and re-entrant borders (0.5 cm. and 0.75 cm. in diameter, respectively), containing in the middle pinhead foci of frank, yellowish-green pus. The pus has not broken through the pia. Pia over right hemisphere contains a slight amount of clear fluid, but is externally almost dry. Effacement of sulci by pressure has just begun. Pia on both sides shows a well-marked injection, with minute, tree-like tracery in the superficial cerebral venules. About some ecchymoses are delicate pink areas of diffused blood pigment (some of which may be of postmortem origin). Vessels at base normal.

Cerebrum. The core of the left occipital lobe is replaced with a walnut-sized mass of loosely clotted blood, resting in a bed of moist, grumous, pinkish-gray detritus. Beyond the zone of disintegration is œdematous white matter, with distinct puncta cruenta and minute hemorrhages. The cortex of the occipital pole is destroyed, and the hemorrhage points also upon the posterior horn of the left lateral ventricle, into which has oozed several cubic centimetres of blood, now clotted *in situ,* with a little staining of posterior portion of choroid plexus. There is no gross evidence of old abscess or other lesion than hemorrhage in this area. It is probable that the hemorrhage is from a medullary branch or branches of the cortical arterial system.

The core of the right occipital pole shows a similar area of hemorrhage (from the medullary branch of the cortical arterial system), thimble-shaped, giving destruction chiefly of white substance with a small portion of cortex. The pia is just tangent to the lesion, which is, therefore, scarcely evident from without.

The substance elsewhere is slightly moister than usual, and both cortex and white matter contain fairly numerous, pinhead, purplish areas of hemorrhage, without evidence of pus. These areas are somewhat more frequent on left side. The substance on section shows a slight retraction of white matter (or release of tension in gray?) and a diffuse appearance somewhat suggestive of encephalitis, but there is no relatively normal white substance with which to compare.

The basal ganglia and lower system are spared from lesion. There are a few ecchymoses in the cerebellum.

Brain. Weight 1265 gms.

Anatomical Summary. Acute endocarditis; acute pericarditis; multiple abscesses of liver, kidney, and thyroid; infarcts of small intestine; acute splenitis; hyperplasia of mesenteric lymph nodes; acute fibrinous pleuritis (left); œdema and congestion of lungs;

acute purulent bronchitis; interstitial orchitis; œdema and congestion of brain; multiple ecchymoses of white and gray matter; abscesses of cortex; hemorrhages into occipital poles (probably from medullary branches of cortical arterial system).

Microscopic Findings. Cultures from heart's blood, pericardium, mitral valve, liver, spleen, kidney, right centrum semiovale, left occipital lobe, and abscess on heel showed staphylococcus pyogenes aureus.

Histological examination of the organs of the trunk showed in the main the lesions diagnosed from gross appearances. The kidney shows a focal chronic interstitial process.

In the subcortical regions of certain foci in the cerebrum and the cerebellum are well-defined abscesses of a characteristic type. A central colony of staphylococci is surrounded by polynuclear leukocytes in a zone, which is in turn surrounded by a zone of fresh hemorrhage. These areas are sometimes a millimetre in diameter, but are, as a rule, merely punctiform. Beyond the lesions there is usually no sign of tissue reaction.

CASE IV.—*Clinical History.* M. M., a woman aged forty-two years, was admitted to Dr. G. C. Sears' service at the Boston City Hospital March 14, 1902. On entrance she was mildly delirious. There was well-marked sclerosis of all palpable arteries, and the heart showed at the apex short systolic and presystolic murmurs, heard also in axilla and back; a systolic murmur was audible at base and in aortic and pulmonary areas. The right lung was dull below the fifth rib in the axillary line (respiration and vocal resonance distant, tactile fremitus diminished). There were friction sounds opposite the right fifth rib. The left base showed many moist rales. Abdomen, dull in flanks, showed fluid wave. There was considerable œdema of ankles and legs. The pupils were equal and reacted normally.

The woman is said to have had influenza three years before, after which she had suffered from dyspnœa, palpitation, and frequent micturition. The menopause had occurred three months before onset of present illness. For four months she had had a slight cough. A week before entrance she had taken to bed with a sharp attack of pain in the right chest, followed by rapid and progressive increase in dyspnœa and increase of cough, with frothy expectoration.

After admission her condition grew worse; she became noisy and garrulous and required restraint. A week after admission she got out of bed during the night and injured her right eye. The upper lid had to be incised some days later, and two drachms of pus were evacuated. Constipation set in, with palpable fecal masses over abdomen. The orbital suppuration grew gradually better, but on the twenty-third day after admission (two weeks after injury to eye) an erysipelas-like condition developed about the eye. Thenceforward the patient gradually failed, and a week later died.

Clinical Summary. Woman, aged forty-two years, just after menopause, with arterial and cardiac sclerosis. Pleurisy with effusion, gradually deepening delirium, injury to eye with suppuration (a week after admission, two weeks after onset of pleurisy), and constipation. Death three weeks after injury to eye, a week after development of erysipelas-like condition about eye, two days less than a month after admission.

Autopsy Findings. The autopsy was performed by Dr. W. R. Brinckerhoff April 14, 1902. The findings in the head were:

Brain. Weight, 1270 gms. Dura and sinuses normal.

Middle Ears. Normal.

On the external aspect of the right temporal lobe is a small abscess (3 mm.) surrounded by a zone of injection. Similar smaller abscesses are present over the vertex. On section, ventricles contain considerable amount of clear, straw-colored fluid. The substance of the cerebrum appears normal. Cerebellum normal. In the middle of pons is a circular area 6 mm. in diameter, which is somewhat soft and of a black color. This area is sharply circumscribed. Its greatest diameter is lateral, not appearing in the adjacent sections 5 mm. apart. The surrounding brain substance appears normal.

Anatomical Summary. Pleurisy with effusion (right side); hydropericardium; multiple abscesses of heart, kidneys, spleen, lung, and brain; ulcerative colitis and proctitis; chronic diffuse nephritis; acute cystitis; uterine fibromyoma; general arteriosclerosis; chronic splenitis; small hemorrhage in pons.

Microscopic Findings. Cultures from liver, spleen, and kidney showed pure growths of staphylococcus pyogenes aureus. Histological examination of the various organs confirmed the diagnosis of septicæmia. No cultures were taken from the brain abscesses, which were saved entire for histological purposes; but there can be no doubt of the relation of the staphylococcus to the abscesses. The special points in the histology of this case are brought out in the following:

The lesions beneath the pia mater of the temporal lobe, for example, consist of a central colony of staphylococci in and about a vessel which is surrounded by a zone of polynuclear leukocytes, often phagocytic for the bacteria. Among the polynuclear leukocytes are numerous larger phagocytes, now of the compound granule type, elsewhere containing chromatic material derived, as a rule, from polynuclear leukocytes. The large phagocytes sometimes contain bacteria as well as remains of tissue cells. Outside the zone of polynuclear leukocytes is a broader zone, consisting almost purely of cells of the phagocyte group, here in most instances of the compound granule type. Beyond these zones of nucleated cells is a zone of pure and well-preserved blood. There is nowhere any notable amount of fibrin. There are in many places small vessels plugged with staphylococci, some of which have grown post-mortem.

The sections from the pontine lesion are of note by reason of the juxtaposition of the fresh hemorrhagic lesions with an older cystic lesion. The older lesion consists of a small cavity, about 2 mm. in diameter, lined by a condensed layer of neuroglia and filled with large, vacuolated phagocytes and granular material. The neuroglia lining is interrupted in places by slender projections due to vessels invested by a thin layer of oval, fibrillated glia cells. The fresh lesions show blood free in the meshes of the tissue, with here and there a large phagocyte and polynuclear leukocyte and without notable amounts of fibrin. The surrounding tissue shows no reaction beyond an increase in the volume of the cell bodies in some neuroglia cells.

CASE V.—*Clinical History.* J. C., blacksmith, of middle age, was admitted to Dr. A. L. Mason's service at the Boston City Hospital December 3, 1897. He was brought to the hospital delirious and unconscious in an ambulance, having fallen in the street.

Physical examination showed the left pupil slightly larger than the right, knee-jerks absent, pulse feeble but regular, chest slightly hyperresonant, pleural rubs in left axilla and lower back, and a temperature of 104°. The urine showed 0.5 per cent. albumin. The patient died the day after admission without change of condition.

Autopsy Findings. The autopsy was performed by Dr. F. B. Mallory December 4, 1897. The findings in the head were:

Brain. On the right side of the pia 3 cm. from the median fissure, and in the sulcus just back of the fissure of Rolando, were three, minute, yellowish specks, apparently miliary abscesses. The surrounding brain tissue was œdematous and swollen and the pia contained minute hemorrhages. In the substance of the brain no lesions could be found anywhere.

Middle ears normal.

Sinuses of nose and the antrum of Highmore on each side were all normal.

Anatomical Summary. Septic infarctions of lungs; metastatic abscesses of kidneys and meninges; acute fibrinous pleurisy; chronic adhesive pleurisy; congestion of lungs.

Microscopic Findings. Cultures from organs of the trunk showed pure growths of the staphylococcus pyogenes aureus, except that from the kidney, which showed also an organism of the colon-typhoid group.

Histological examination confirmed the diagnosis made from gross appearances. The liver shows some cellular infiltration of the portal spaces and central congestion.

The histological picture presented by the brain varies from a simple meningitis to a diffuse meningoencephalitis. The simple meningeal inflammation consists of an exudate of polynuclear leukocytes, more thickly into the proximal meshes of the pia mater. There is strikingly little blood and a small amount of fibrin in this lesion. There are fewer meningeal phagocytes than usual; but a few lymphatic clefts are filled with such cells containing fragmented polynuclear leukocytes. The exudate follows the cortical arteries into the brain substance in some cases as far as the white matter. The subpial neuroglia and the pyramidal cell layers are for long distances dotted with polynuclear leukocytes of fairly even distribution. It is unusual to find polynuclear leukocytes in apposition with nerve cells. The nerve cells are slightly swollen. The bodies of the neuroglia cells are, as a rule, invisible; but some of the cells of the subpial layer approach the astrocyte in type.

CASE VI.—*Clinical History.* A. M., an Irish woman aged thirty-three years, was admitted to Dr. J. N. Coolidge's service at the Boston City Hospital June 15, 1904. On entrance she was delirious, half-conscious, and unable to answer questions. There was convergent strabismus and a choreiform or athetoid tendency to co-ordinate movements of both arms. Nothing further was discovered in the physical examination to throw light on the condition. The present illness was said to have lasted ten days, setting in with vomiting, which continued for five days. The strabismus was developing meanwhile, and the twitchings became well marked. She was sleepless and complained of soreness in the abdomen. For years she had been addicted to the use of alcohol, often to excess. The patient died five days after entrance. The choreiform movements persisted until death. The convergent strabismus became more marked. Stiffness of neck developed. The reflexes remained normal.

Clinical Summary. Woman, aged thirty-three years, with history of abuse of alcohol, died in delirium fifteen days after onset of an attack of choreiform character, with convergent strabismus, insomnia, and normal reflexes. Onset with vomiting, lasting five days.

Autopsy Findings. The autopsy was performed by Dr. S. B. Wolbach June 21, 1904. The description of the head by one of us (E. E. S.) follows:

Head. Scalp normal; skull symmetrical; frontal suture effaced. Superciliary ridges and frontal eminences ill-defined. Calvarium opaque by transmitted light and everywhere moderately thickened. The thickening affects chiefly the inner table, and is least marked at the bregma, where the internal surface presents a shallow, diamond-shaped depression corresponding to the anterior fontanelle. The frontal bone shows marked symmetrical thickening, which transforms inner arc to an oblique flat surface, on which there is a slight groove for the superior longitudinal sinus and a few narrow depressions for the meningeal vessels. At a point 4 cm. from the orbit the bone is 1.5 to 2 cm. thick. The diploë is nowhere well marked. The frontal bone is ivory-like on section and of the consistence of the petrous bone. Dura normal. The dura beneath frontal bone is readily separable from the inner table. Sinuses and meningeal veins contain fluid blood. Pial vessels everywhere injected. Arachnoidal villi well developed. Pia of vertex œdematous. Substance moist. Everywhere elastic except in an ill-defined area, including second right temporal convolution. The cortex and underlying white of this region are plastic and readily crushed; the puncta cruenta of the white matter are distinct, and there are a few minute, perivascular hemorrhages. Co-ordinate areas in the left hemisphere are equally moist; but the gray matter does not bulge from the plane of section. The rest of the centrum semiovale shows no more than œdema.

The frontal convolutions are fairly symmetrical. There is no microgyria and no narrowing of gray matter, but there is a slight increase of consistence in the frontal gyri on comparison with, for instance, the occipital gyri. The frontal and especially the prefrontal region as a whole may be looked on as undersized. Rest of encephalon and spinal cord show less œdema than the hemisphere and no further gross lesion.

Middle ears normal.

Anatomical Summary. Œdema and congestion of lungs; chronic fibrous pleuritis (left); œdema of pia; cerebral œdema; focal softening of right second temporal convolution (encephalitis); frontal lobes undeveloped; thickening of cranium (most marked in frontal bone).

Microscopic Findings. Cultures from organs of the trunk remained sterile. Culture from the white matter beneath the second right temporal convolution showed staphylococcus pyogenes aureus, together with a few colonies of similar appearance which never assumed a golden-yellow color (staphylococcus pyogenes albus?). A culture of the staphylococcus pyogenes aureus derived from this case was used in a portion of the inoculations described below.

Examination of the organs of the trunk showed nothing adequate to account for the history of the case. The lung shows a few *Herzfehlerzellen* in some alveoli and a few bronchi plugged with polynuclear leukocytes in good preservation and without bacterial inclusions. The spleen shows an unusually high percentage of polynuclear leukocytes and fairly numerous eosinophilic leukocytes in the pulp, but is otherwise not remarkable. The liver is slightly fatty; some of the cells central in the lobules are lace-like. The kidney shows a few slender casts in the tubules of the pyramids. Otherwise both the organs mentioned and the others examined show little that is noteworthy.

Co-ordinate places in the hemispheres were examined to detect the extent and nature of the inflammatory process suggested by the gross appearances and the bacterial findings. The two sides are distinguished by the fact that, in the section taken from the cortex and white matter of the right temporal lobe, there are numerous small collections of blood globules, with a few polynuclear leukocytes lying in the meshes of the arterial adventitia. There seldom occur, however, hemorrhages of any great volume. Blood rarely occurs free in the tissue. On comparison with tissue from the opposite hemisphere it is found that very many more distended capillaries have become visible in the cortex and notably in the subcortical region of the right temporal lobe. Several of these capillaries are found packed with polynuclear leukocytes. The neuroglia shows no pertinent differences on the two sides; the subpial glia of the left hemisphere appears denser in structure than in the right in the places examined. Numerous nerve cells are contracted and somewhat densely staining by several of the technical methods employed (eosin and methylene blue, aniline blue connective tissue, and phosphotungstic-hæmatein methods, for example). These cells are possibly more numerous in the left hemisphere than in the right in the places examined. These latter changes are certainly not beyond the range of artefact and are scarcely entitled to specific importance on account of the omnipresent œdema. Yet these cells recall the cells found in certain foci of our experimental material. The cerebellum and the rest of the nervous system as far as examined showed no noteworthy lesion. A few capillaries in the choroid plexus contain numerous polynuclear leukocytes; there is a much smaller number outside the capillaries and none beyond the ependyma.

General Clinical Summary. From the histories detailed above the following *résumé* has been drawn:

Three of the patients were male, three female. Their ages varied from five to fifty-five years.

In every case, excepting Case V., whose past is unknown, there is a history of antecedent disease; thus Case I. was convalescing from scarlet fever; Case II. was five weeks recovered from diphtheria and had a chronic endocarditis of long standing; Case III. was under treatment for chronic urethritis; Case IV. had pleurisy with effusion and was but three months beyond the menopause, and Case VI. had a history of excess in alcohol of many years' duration.

The onset was in three cases sudden (hemiparesis and unilateral convulsions in Case I.; chilly feelings and frontal headache followed by ecchymoses in Case II.; malaise, manifold pains, ecchymoses, and cerebral symptoms in Case III.). Case V., in which the onset is unknown, was in all ways fulminant. In Case IV. the symptoms gradually supervened upon the pleurisy and the orbital suppuration. Case VI. showed a gradual onset.

The syndromes as a whole were of pronouncedly cerebral type in Cases I. and VI., of meningitic trend in Cases II. and III., of septicæmic character in Case IV. Septicæmia could be suspected in all three cases (II., III., IV.) in which superficial ecchymoses or suppuration became prominent.

The temperature varied for the various cases: at times 103° and 104° for cases III. and V.; the temperature in cases II., IV., and VI. was never high and frequently subnormal.

The pulse was in no case subnormal, and, as a rule, ranged above 100. The respirations were, as a rule, increased.

The duration of the encephalitic symptoms cannot in all cases be closely reckoned: Case III., three days; Case IV., one week (after development of erysipelatoid condition) or three weeks (after injury to eye); Case II., eight days; Case I., two weeks; Case VI., fifteen days; Case V., unknown. Thus those cases were of longer duration in which the cerebral syndromes were most clearly marked.

General Anatomical Summary. Of the gross findings at autopsy the following are to our present purpose: chronic lesions which might correspond with greater likelihood of bacterial infection were found in several cases; thus, the remains of scarlet fever in Case I., chronic endocarditis in Case II., arteriosclerosis in Case IV.

The phenomena of general infection were found in Cases II., III., IV., and V. Comment is made below upon the correlation of pulmonary lesions with our cases.

The distribution of the brain lesions is as follows:

Four cases (I., II., III., IV.) showed areas of frank and somewhat voluminous hemorrhage, as a rule involving primarily the subcortical region (of the vertex in Case I., of the occipital lobes in Cases II. and III.), and in Case IV. affecting the pons.

Three cases (III., IV., V.) showed multiple ecchymoses and small abscesses of the cortex or subcortical region, with or without gross evidence of surrounding œdema.

In three cases (I., V., VI.) œdema of pia mater was remarked.

In two cases (II. and III.) there was noted an effusion of blood into the lateral ventricles; and in these cases the convolutions were flattened.

In two cases (IV. and VI.) in which the temporal lobe was involved the middle ears showed no lesion. The mucosæ of the head play no such role in this kind of encephalitis as in the massive brain abscesses made familiar by Macewen.

General Summary of Microscopic Findings. The staphylococcus pyogenes aureus was found in all cases in culture post-mortem, generally distributed in five cases, in the brain alone in Case VI. The diagnosis of general infection, at least at the time of death, seems warranted in the first five cases. Case VI., in all ways unusual, may possibly be interpreted as showing the first stage of a massive brain abscess; but the middle ear showed no lesion at autopsy. The atria of infection remain obscure in Cases V. and

VI. In Cases II., III., and IV. acute endocarditis was found; and, although in none of these cases is the chain of evidence entire, there were present in all three adequate primary lesions (suppurating surgical wound in Case II., chronic urethritis in Case III., colitis in Case IV.).

The microscopic findings in the organs at large call for little comment. Focal pulmonary lesions were either grossly prominent or made out microscopically in all six cases. There was pus in the bronchi of Cases III. and VI., bronchopneumonia in Case I., and there were septic areas of hemorrhage in the lungs of Case II., septic infarction in Case V., and multiple abscesses in Case IV. This coincidence of pulmonary and brain lesions is certainly of clinical importance. A similar coincidence was noted at least as early as the sixties of the last century.[1] Compare also the production described below of meningitis and meningoencephalitis in the guinea-pig by intrapulmonary inoculations. We are not prepared at present to regard this coincidence as a matter of cause and effect.

The microscopic findings in the brains of this series of cases present more features in common than the gross findings. Thus, whereas miliary abscess, punctiform or massive hemorrhage, and ill-defined red softening form quite diverse gross pictures, the microscopic pictures form unitary series or are well-nigh interchangeable.

It is, moreover, by no means scholastic to insist that too close lines cannot be profitably drawn between meningitis and encephalitis. The word "extension" has gained so wide a vogue that one forms the idea that, although a process may extend, the diagnosis somehow should not extend *pari passu.* Meningitis by extension from abscess and encephalitis by extension of pial inflammation are processes of importance, though charged with being merely secondary. It is these secondary phenomena, in especial the encephalitic ones, which, in the cured cases, may afford a basis for our so mysterious scleroses.

The inflammation of meninges and cortical and subcortical substance in man produced by the staphylococcus pyogenes aureus is distinctively hemorrhagic. Very little fibrin is formed in these lesions. The bleeding continues in some cases until stopped by intracranial pressure. Small vessels are, as a rule, affected.

The typical picture is of a central colony of staphylococci in and near a vessel surrounded by zones of polynuclear leukocytes, large phagocytic cells, and blood. Dying nerve cells are sometimes included in the lesion. The neuroglia cells are slightly active about some of the lesions. Fibril production is absent. The myelin sheaths stain well by Weigert to the edge of the lesions, but show fatty changes in Marchi preparations, for a short radius round about. Prominent in these lesions are the fat-containing and leukocyte-containing phagocytes of the type so often found in all kinds of cerebral lesions. The accumulation of these was in no other case so massive as in Case I.; but they are omnipresent. Their frequency and distribution are such that many foci of these lesions look, in accordance with our usual ideas, to be of long standing.

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[1] Biermer, Zur Theorie und Anatomie der Bronchienerweiterung, Virchow's Archiv, 1860, xix. S. 244.

Experimental Material. As supplement to the histological work on the lesions in man, a series of inoculations of the staphylococcus aureus was made in guinea-pigs and rabbits. Several strains of staphylococci were used, derived from various lesions, including the focus in Case VI. It was found best to employ one species of animal for serial work; and the guinea-pig was chosen. It is easy to include in single sections meninges, substance, and ventricle of the guinea-pig brain. Several methods of inoculation were employed, as beneath the skin, into the lung, through the ear-plate, and beneath the dura. The guinea-pigs stood the inoculations well and, after recovery from chloroform anæsthesia, as a rule showed no sign of disease up to the time of examination. In some cases they were overwhelmed by the septicæmia. The fatal results are apparently more a matter of individual pig than of culture. The most convenient method was found to be the method by intrapulmonary injection.

By intrapulmonary injection of 0.5+ c.c. of a twenty-four-hour bouillon culture of the staphylococcus of the strains used one is almost certain to produce exudation into the meninges of the guinea-pig. Of this there will probably be no clinical evidence. But examination of the brains of the pigs at suitable intervals will show lesions of fairly rapid evolution. These inoculations have been controlled by subdural inoculations, with examination at similar intervals.

As early as six hours after intrapulmonary inoculation the meninges may show evidence of diapedesis of blood and exudation of polynuclear leukocytes of quite focal character. The ependyma remains clear, and no changes can be detected in the brain substance.

By twelve to fourteen hours after inoculation exudation through the ependyma is likely to be well under way.

Twenty-four hours after inoculation the vessels are injected, and blood and occasional polynuclear leukocytes are likely to be found in the pial meshes. The chief sign of inflammation, however, is the frequent demonstration in the vessels of a row or thin lining of leukocytes in the inert layer.

In one instance after intrapulmonary injection the guinea-pig immediately became paraplegic and was killed after twenty-four hours. The brain showed ependymitis, very marked meningitis, and the most extensive exudation of leukocytes into the brain substance which we were able to procure in the intrapulmonary inoculations. In this case leukocytes were very frequently seen in juxtaposition with the small pyramidal nerve cells. The same phenomenon was found later in the intrapulmonary series (although never so markedly as in this case) and is focally present in several instances in cases of subdural inoculations examined after two or three days. It is perhaps not necessary, in accounting for this occurrence of leukocytes near nerve cells, to invoke a richer lymph system for the guinea-pig brain than for the human brain. Possibly the leukocyte can more easily wander through the substance of the guinea-pig brain because it is less densely fibrillar than that of man.

Forty-eight hours after inoculation, the emigration of leukocytes into the tissue beneath the ependyma is already marked, and numerous examples can be found of leukocytes in apposition with nerve cells.

The cases examined three days after inoculation show meningitis, encephalitis, and ependymitis at their height. The controls by subdural inoculation show far more intense diffuse processes. The three-day subdural material can be recommended for study of the cells in the lesions produced by this organism.

In material examined four and five days after inoculation the exudate is already altered by the appearance of fairly numerous cells of the lymphocyte series and a number of cells phagocytic for cell detritus.

Six days after inoculation the lesions found are meningitis and pyocephalus, due largely to exudation from the choroid plexuses. The cells found are chiefly of the polynuclear amphophile type. Mononuclear cells phagocytic for leukocytes occur. The meningitis is rarely so voluminous as the ependymitis. Numerous polynuclear leukocytes follow the cortical vessels; and it is not unusual to find leukocytes of the amphophile type in close apposition to nerve cells, as well as free in the tissue of the upper cortical layers.

The brain of the guinea-pig nine days after inoculation shows little exudative process except about certain vessels, where rare polynuclear leukocytes occur with fairly numerous cells of the mononuclear series. Occasional cells phagocytic for chromatic material occur, besides a few pigment-bearing cells. The exudate is, as a whole, slight.

Few traces of inflammation are demonstrable in the brain of a guinea-pig one month after inoculation. The brain substance shows no alteration beyond a few areas of chromophilic nerve cells mentioned below. Neuroglia fibrillæ are demonstrable beneath the pia, but in quantity which is within the normal limits for the guinea-pig by the methods used. The ependyma shows no change. The pia mater contains a few pigment-bearing phagocytes, a few lymphoid and plasma cells, and relatively many eosinophilic polynuclear leukocytes.

The examinations were throughout controlled by cultures from various organs, the brain, and the site of operation in the subdural inoculations. A surprising proportion of negative cultures was obtained from the brain even where lesions of the appropriate age could be determined. The tenuity of the lesion makes searing risky. Perhaps cultures from the ventricle are preferable in cases where the process has reached the ventricle. The above descriptions have been founded on cases in which the bacterial diagnosis was secure. The organs of the trunk were examined in many cases to make sure of the pyæmia.

Mention may be made of a frequent lesion in the guinea-pig brain which remains obscure. To be distinguished sharply from the focal occurrence of condensed, deeply staining nerve cells, and from the occurrence in compressed material and at the edges of some sections of groups of similar cells which are more or less clearly a product of technical error, are certain foci of contracted, angular or subangular, deeply staining nerve cells of the cortex. In one case there were deposited in the cell bodies of one of these chromophilic foci dots staining by the phosphotungstic-hæmatein method. These foci of chromophilic cells occur, as far as we have yet found, without definite relation to the bacterial inoculations, but are not characteristic of the brain of normal pigs. The process is a little more frequent in groups of Purkinje cells.

Resume. 1. The staphylococcus pyogenes aureus produces in the meninges and brain substance of man a type of inflammation in which hemorrhage is prominent.

The picture post-mortem in man varies from red softening or multiple ecchymosis and small abscess to frank and sometimes voluminous hemorrhage. The site of election for the hemorrhagic lesions is the subcortical region, supplied by the long or medullary branches of the cortical vascular system.

The histological picture varies from diapedesis and slight leukocyte emigration to abscess and acutely destructive hemorrhage with phagocytosis. Collections of mononuclear cells phagocytic for cells and cell detritus often quite obscure the acute inflammatory appearance of the lesion.

Six fatal cases in man were examined, all but one cases of general infection with the staphylococcus aureus.

A history of antecedent disease was the rule. The syndromes, which were chiefly of sudden onset and rapid course (three to fifteen days), were pyæmic, meningitic, or cerebral in type. The cases of slower course were the most plainly cerebral.

2. The staphylococcus pyogenes aureus produces in the brains of guinea-pigs an inflammatory process which tends to subside within a limited period (two weeks), and, as a rule, remains without clinical signs throughout.

No hemorrhages other than miliary perivascular ones were observed in the guinea-pig. The lesions are seldom grossly evident.

The cell pictures are of meningitis (discernible in six hours), ependymitis (twelve to fourteen hours), and exudation into the brain substance (twenty-four to forty-eight hours).

The four and five day cases show numerous cells of the lymphocyte series as well as mononuclear cells phagocytic for exudative cells. Examples of such phagocytic cells have been found as early as twenty-four hours after inoculation.

The exudation into the meninges is discernible earlier, and its traces are demonstrable later, than are the processes in the ependyma and the encephalon; but the meningitis is never so extensive or striking a process as the encephalitis or the choroiditis.

In two weeks to a month there is little sign of the previous infection.

3. The staphylococcus pyogenes aureus, of the strains and in the doses experimentally used, produces in the guinea-pig a curable encephalitis, that is a process which in logic is termed reversible. The same organism produced in our human cases extensive brain lesions which surely look as a group irreparable. Perhaps, however, there are in man also certain cases of encephalitis which reverse themselves, and which in their course are taxed with being "functional" diseases and furnish "functional" symptoms during and after tissue repair.

We wish to thank Drs. Mason, Shattuck, Sears, and Coolidge for the use of their clinical records, and Drs. Brinckerhoff, Thompson, and Wolbach for the anatomical data in their autopsies. Drs. Councilman and Mallory have looked over the histopathological work, and Dr. W. N. Bullard has interested himself in its neurological aspect. The work was done under the Bullard Gift to the pathological department of the Harvard Medical School for 1904.

IV

A CASE OF GLIOMA OF THE PINEAL REGION.

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Following is a case of psammoma of the pineal region. A study of the cell-picture and of the intercellular contents has aligned the tumor with the gliomata rather than with the sarcomata. The cell-picture varies locally within the growth, presents unusual multinucleate structures, and is altogether more multiform than is the rule with glioma. Clinically the case is quite undefined, but scarcely more so perhaps than most cases of the pineal-quadrigeminal group of cerebral tumors.

I. Clinical History.

P. H., an Irishman of forty-four years, was transferred March 14, 1904, from the Lawrence Almshouse to the Danvers Insane Hospital. He was fairly well nourished, but oldish-looking and weakly. He was unable to stand or walk alone. His gait, when supported, was feeble, tremulous, and somewhat propulsive in character; the left leg dragged a little. There was a slight tremor of the hands; the left hand grasp was a little weaker than the right. There was a coarse tremor of the tongue. Of the reflexes, the knee-jerks were much increased; and the pupils, which were small and equal, failed to react to light. The Achilles, triceps, and wrist reflexes were present. The sensations were normal. The apex-beat was visible in the sixth interspace one inch outside the nipple-line; there was a soft systolic murmur at the apex. The rest of the physical examination was negative, except for a degree of peripheral arteriosclerosis.

The patient's manner was agreeable, and he conversed willingly with the examiner. His answers to questions, though often incorrect, were as a rule relevant. His speech was somewhat thick. He was disoriented for time and only partially oriented for place. He was deficient in school knowledge and in ability at simple calculation. The hand-writing was very defective. His memory was unreliable. There was no evidence of hallucinations, delusions, or romancing tendency.

The patient was under observation until death, May 5, 1904, and, until a few days before death, little change was noted in him. He remained bed-ridden and untidy. During the first days of May he developed a temperature varying from 102 to 104.2, and relapsed into a comatose or semi-comatose condition, varied by general convulsions.

Little as to his antecedents could be discovered. He had been a worker in the mill-towns in northeastern Massachusetts since his emigration from Ireland in 1890. His family and personal history was negative. He used alcohol to some degree. His inability to walk dated from what he termed a " shock " seventeen months before his death.

I am indebted for the above notes to Drs. H. W. Mitchell and H. M. Swift, physicians to the Danvers Insane Hospital.

CLINICAL SUMMARY.

An Irish mill-worker of forty-four years, with moderate arteriosclerosis. Mental changes of unknown onset and duration (patient an almshouse transfer) : disorientation, defective memory, and some general deficiency. Inability to walk unsupported, (dating from a " shock " seventeen months before death) and weakness of legs, with slight dragging of left leg. Tremor of hands, with somewhat weaker grasp on left side. Stiff pupils. Increased knee-jerks. Signs and symptoms stationary. Death in the eighth week of hospital observation, from an intercurrent pneumonia.

II. Gross Findings.

Body well built and well nourished. Skin pale. Face pitted as from variola. Deep cicatrices on outer surface of right thigh and leg. Pupils equal, 5 mm. in diameter.

Cavities of trunk not remarkable, except that upper right pleura is effaced.

Heart.—Wt. 400 gms. Ecchymoses beneath epicardium, particularly over right ventricle. Valves of normal appearance, measure: Tricuspid valve 14.0 cm., pulmonary valve 9.2 cm., mitral valve 11.5 cm., aortic valve 9.0 cm. Muscle-substance dull colored and flabby. Left ventricle measures 1.5 cm., right ventricle 0.3 cm. in thickness.

Lungs.—Left lung edematous, posteriorly shows post mortem congestion. Right upper lobe solid and red-gray with a finely granular surface of section and numerous vascular points. The parietal pleura and subpleural fat are removed with the lung which is overlaid with a thin layer of fibrin. Lower lobes edematous and injected.

Spleen.—Wt. 140 gms. Capsule normal. Substance soft and pulpy, obscuring trabeculæ and Malpighian bodies which are enlarged.

Liver.—Wt. 1640 gms. Section surface broadly mottled with gray and reddish brown. There is a finer mottling with dull, dark red and lighter reddish-gray, which corresponds with the lobules. Substance friable. *Gall Bladder* normal.

Kidneys.—Wt. 590 gms. (right 370; left 220). Strip readily. Subcapsular surface finely irregular but smooth and glistening. Cortex slightly wider than normal and opaque yellowish-gray in color. Conspicuous injection. Glomeruli very distinct. Three subcapsular cysts, 2-5 cm. in diameter, in right kidney.

Other organs and tissues of trunk and extremities not remarkable. The *Aorta* shows slight sclerosis.

Head.—Calvarium shows thin tables and soft, deep red diploe. *Dura Mater* tense, non-adherent. *Sinuses* normal. Arachnoidal *Villi* moderately developed. *Pia Mater* delicate and clear over convexity, but over base and cisterna cloudy. About the superficial origins of the cranial nerves and along upper margin of pons there is an increase of connective tissue. *Convolutions* flattened and velvety. Section through the stem at the anterior border of the pons shows a *Mass* springing from and continuous with the pineal gland, lying in third ventricle and aqueduct of Sylvius. The mass is soft and reddish-gray; the free surfaces are granular and hummocky; the other surfaces are moulded smooth by the ventricle and aqueduct walls. Farther sections, after hardening in formalin, show that the mass begins posteriorly in substance resembling the pineal body, gray and grit-containing, and stretches forward, mainly to the right of the median line, to a point just anterior to the gray commissure. The mass lies free in the third ventricle or presents here and there light adhesions with the ependyma. Posteriorly the mass bulges beneath the splenium of the corpus callosum and is rather firmly adherent to the pia as far back as the groove between the anterior and the posterior corpora quadrigemina. The mass is of fairly homogeneous appearance. The part continuous with pineal body has an injected border.

The lateral *Ventricles* are symmetrically dilated.

The canal below the mass is not evident.

The autopsy was performed by Dr. A. M. Barrett, to whom I am indebted for permission to report the case, for the materials of the above description, and for numerous suggestions.

ANATOMICAL SUMMARY.

Death from right upper lobar pneumonia, with fibrinous pleuritis, and acute splenitis.

Moderate arteriosclerosis.

Chronic diffuse nephritis.

Hypertrophy and dilatation of heart.

Neoplasm springing from pineal gland, occupying posterior half of third ventricle, anterior orifice of aqueduct of Sylvius, and the space beneath velum interpositum as far back as posterior corpora quadrigemina. (Figs. 1 and 2.)

Dilatation of lateral ventricles of brain with internal hydrocephalus and flattening of cerebral convolutions.

Chronic fibrous leptomeningitis at the base of the brain.

III. Microscopical Findings.

Cultures from the trunk organs proved sterile, except from the *Lungs* which contained: right, staphylococcus pyogenes aureus and pneumococcus; left, staphylococcus pyogenes aureus, pneumococcus (?), and a few colonies of a bacillus of the pseudo-diphtheria group.

Microscopical examination of the organs of the trunk chiefly confirmed the gross diagnoses. The pneumonic lung shows an exudate mainly purulent, with considerable edema, small hemorrhages and numerous bacteria, both cocci and bacilli, the latter resembling the bacilli found in culture from the left lung. The heart shows brown atrophy. There is no great evidence of general arteriosclerosis. The kidneys show cloudy swelling and slight fibrous overgrowth in some foci of the cortex with atrophy of a few glomeruli. The liver shows a very mild grade of portal cirrhosis.

The finer structure of the tumor was studied in various regions by a number of methods and was found to differ appreciably on passing from the line of origin to the free-hanging intraventricular parts. The tissue throughout is supplied with well-formed vessels, and there is nowhere any notable hemorrhage or necrosis.

The most striking thing in the microscopical picture is the great number of lime deposits, which range in size from a few micra to above a millimeter in diameter, exhibit in places a roughly concentric layering, and are surrounded by neuroglia fibrillæ.

The deposits, when teased out from the tumor and treated with dilute HCL, evolve bubbles of gas. Sheaves of acicular gypsum crystals form on treatment with dilute H_2SO_4. The distribution of the lime seems to be characteristic in that, on passing toward the outlying parts of the tumor, fewer and smaller masses appear. No masses are detectable in the plug of tumor which has lodged in the aqueduct of Sylvius, and very little lime can be found in the mass which fills the third ventricle.

The tumor is everywhere rich in cells, but in the outlying and intraventricular parts exhibits very little intercellular substance of any sort. Nevertheless, in portions of the tumor well-penetrated by the fixative (formaldehyde and Zenker's fluid were used), a few fibrillæ can be demonstrated by various methods. The fibrillæ are demonstrable in great quantities in the cell-masses near the line of attachment of the tumor. They are fine and of fairly even diameter, long, and smoothly curving, and enclose the cells in a fashion typical for neuroglia fibrillæ. They surround the lime deposits in some cases quite smoothly and evenly (Fig. 5), but there is never any heaping-up of coarse fibrillæ about the masses such as may be found in the normal pineal body of the adult about the similar deposits there laid down (Fig. 6). The fibrillæ can be brought out by Weigert's neuroglia stain and by Mallory's phosphotungstichematteinin stain for neuroglia. They stain like neuroglia fibrillæ with Mallory's aniline blue stain for connective tissue.

The cell picture is multiform. Corresponding with the development of the fibrillæ there are numerous cells in the tumor which somewhat closely resemble the active neuroglia cells often found in the cortex beneath the pia mater, or elsewhere in or about cortical lesions. In some cases the fibrillæ lie in apposition with processes of the cell body or in apparent continuity therewith. The number of the astrocyte forms is, however, relatively low.

More characteristic is a multiformity and irregularity in size of cell and nucleus which offhand suggests a classification of the tumor with the sarcomata. The greater portion of the tumor is composed of cell-masses which, were it not for very sparing fibrillæ reacting like neuroglia fibrillæ, would readily warrant the diagnosis of sarcoma. The cells are small; the cell body slight; the nuclei range from the size of lymphocyte nuclei to twice or three times as large. The smaller nuclei are spherical; the larger ones irregularly rounded or oval. The nuclei have well-marked outer borders and one to several nodal points of deeply staining chromatin centrally placed. In places are larger cells with four or five peripheral nuclei, oval with tips touching or overriding. The central cytoplasm of these structures is hyaline. There is a suggestion of central dots in a few such structures. In the portion of tumor described above no mitoses are demonstrable.

In some areas, however, not only mitoses but also very numerous multinucleate cells occur. In these areas, which are not frequent and run irregularly through the middle portion of the tumor, the tissue is more open and has fewer well-formed vessels. The structures regarded as mitoses are highly convoluted, deeply staining, and voluminous, occupying spaces as large as many of the multinucleate cells. Besides the mitoses are numerous cells with irregular nuclear forms. The nuclei are multilobate or actually multiple. The lobes or separate nuclear elements are of various size, and are sometimes drawn into bizarre or even ameboid shapes. One cell of this group, measuring 65 × 45 micra, shows five large, peripherally disposed nuclei connected by smoothly tapering bridges, which radiate out from a center (Fig. 7). This sort of structure is approached in several other examples, wherein pale bands are set as if on the stretch between nuclear lobes or elements, and are differentiated from the rest of the cytoplasm chiefly by optical characters.

SUMMARY OF MICROSCOPIC FINDINGS.

Lobar pneumonia. Brown atrophy of heart. Slight chronic interstitial nephritis and hepatitis.

Psammoma of pineal region: New growth well supplied with vessels, without hemorrhage or necrosis. Lime-deposits surrounded by neuroglia fibrillæ. Variable content of fibrillary intercellular substance reacting like neuroglia fibrillæ. Cell-picture various: Astrocytes, smaller and larger cells resembling those of sarcoma, mitoses, large cells with multilobate, bizarre, and multiple nuclei.

IV. Remarks.

There are in the literature somewhat over fifty accessible observations upon tumors (and cysts) arising in the pineal region. Of these a few only relate expressly to glioma or gliosarcoma. No plates accompany these accounts, which in the main antedate the neuroglia knowledge of the last decade; and there is no means of divining the intercellular structure from descriptions of cell-pictures which fit the diagnosis equally of glioma and of sarcoma. It is nevertheless probable that a number of these cases were truly cases of pineal glioma and that further undoubted cases will be recorded if interest can be stretched to include a differentiation of the intercellular substances. It is moreover plain that, if there be a type of psammoma related to the sarcomata or endotheliomata, there exists in any event also a type of sand tumor belonging to the gliomata.

EXPLANATION OF FIGURES.

Fig. 1.—Frontal section 8 cm. behind anterior pole. Note flattening of gyri, dilatation of lateral ventricles, and tumor in third ventricle.

Fig. 2.—Section shows posterior commissure in oblique section, with third ventricle above and Sylvian aqueduct below, both occupied by a continuous tumor mass.

Fig. 3.—Low-power view of tumor against the buckling wall of Sylvian aqueduct.

Fig. 4.—Low-power view of tumor showing masses and space occupied by large mass of lime deposit. Layer of condensed neuroglia below.

Fig. 5.—750 diameters. Detail from tumor showing neuroglia fibrillæ around lime deposit.

Fig. 6.—750 diameters. Detail from adult pineal body showing coarse neuroglia fibrillæ amongst lime deposits.

Fig. 7.—750 diameters. Bizarre multinucleate cell from tumor.

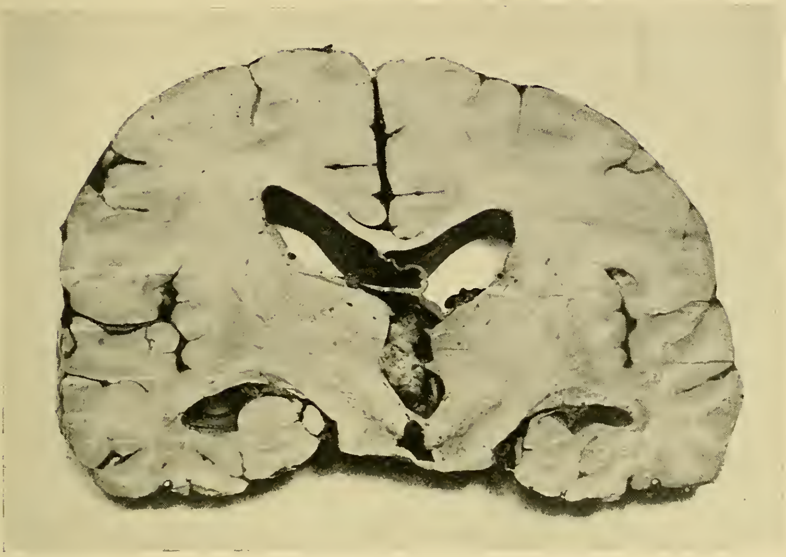

FIG. 1.

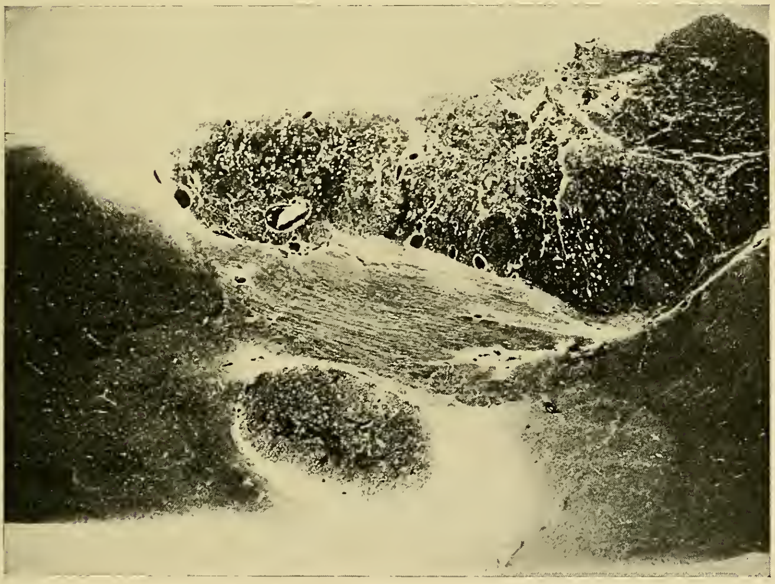

FIG. 2.

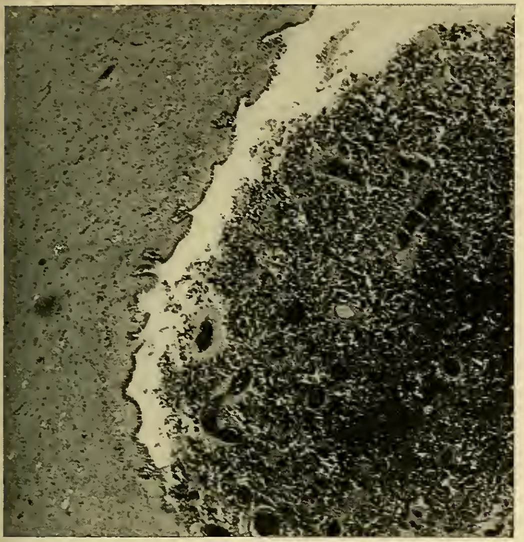

FIG. 3.

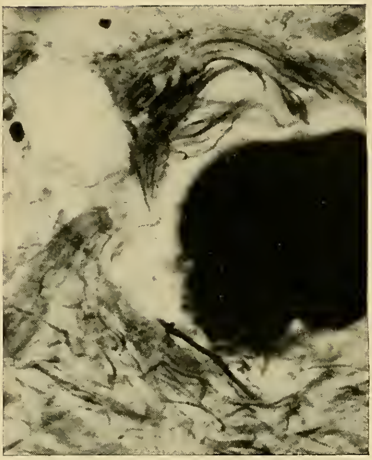

FIG. 5.

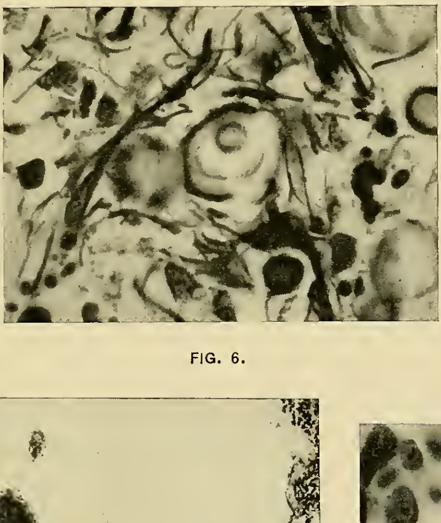

FIG. 6.

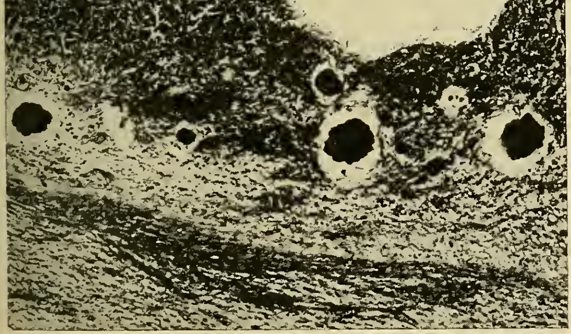

FIG. 4.

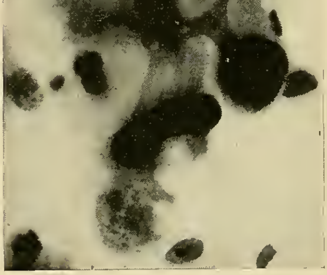

FIG. 7.

V

A Case of Cholesterin Stones in the Brain and Cord.

A CASE OF CHOLESTERIN STONES IN THE BRAIN AND CORD.*

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BOSTON.

Following is a case of multiple cholesterin concretions found at autopsy in the brain and cord of a man who showed in life no signs referable thereto. About the masses there was a fibrillary overgrowth of neuroglia.

The patient was under clinical observation at the Boston City Hospital for a little over three weeks in the spring of 1904, on the medical service of Dr. C. F. Withington, whom I wish to thank for the use of his records. The patient was a man of 56, with extensive peripheral arteriosclerosis. For the most part he presented a plain history of cardiac disease growing worse: orthopnea, dyspnea, cyanosis, edema, all coming on in irregular spells, together with gradual enlargement of the heart area and feebleness of heart action, slight albuminuria, a fairly constant demonstration of a soft blowing systolic murmur at the apex transmitted to the axilla, and gradual development of dullness in lower backs. There were no signs directly referable to lesion of the nervous system. A frost-bite of the previous winter had failed to heal well in the right foot. He died a little unexpectedly during a slight apparent improvement in his cardiac symptoms.

The autopsy showed general and extensive arteriosclerosis. The coronary arteries were extensively yellowed and stiffened. The aorta showed diffuse sclerosis with calcification. The sclerosis of the circle of Willis was unusually extensive; and its primary and secondary

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* From the Pathological Laboratory of the Boston City Hospital.

* Read in the Section on Pathology and Physiology of the American Medical Association, at the Fifty-sixth Annual Session, July, 1905.

branches were involved. The heart showed considerable hypertrophy (weight, 615 grams) and diffuse yellowish thickenings of the mitral leaflets. The mitral orifice measured 11.5 cm.; the other valves were not abnormal. The heart muscle showed fine fat droplets in a very few fibers by the Scharlach R. method. Fresh extensive infarctions of the kidney were found, due either to thrombosis or to emboli, which had become in part organized. A hemorrhagic wedge-shaped area in the lower lobe of of the right lung was covered with fresh fibrin. The lungs in general were edematous and congested. The trunk showed little else abnormal save a fibrous pleurisy of the left side and chronic thickenings about the spleen and the liver. The organs of the trunk were examined and the liver. The organs of the trunk were examined by Dr. C. W. Duval, whom I wish to thank for his records.

The findings in the head were as follows:

Scalp, calvarium, dura normal. Sinuses contain fluid blood. Pia edematous, notably over vertex. Strips readily. Superficial veins contain no great amount of blood. Carotids yellow and stiff almost uniformly. Circle of Willis, with primary and sometimes secondary branches, focally yellow and stiff. Substance shows on external palpation no great variety of consistence. The brain is slightly moister posteriorly. The gyri are fairly firm. On section the substance of the anterior portions of the centrum semiovale in both hemispheres is of normal consistence. The posterior portions of the centrum semiovale are moister and softer than in front; brain substance clings to the knife on section. The edema and softening are more marked on the right hemisphere. At the junction of the gray and white matter of the posterior portion of the left middle temporo-sphenoidal convolution is a coherent, gritty, solid sliver of yellowish-gray material 1.5x1.0x0.3 cm., tightly adherent to the surrounding tissue. There is a similar spheroidal mass about 1 cm. in diameter, imbedded in the gray matter of the right inferior frontal convolution. Adjacent to this inferiorly about 1 cm. distant is a purplish-red, slightly translucent, smoothly cutting and slightly bulging area 1 cm. in diameter, in the inner zone of the cortex. Next this is a small indefinitely bounded area of moist, grumous, opaque, yellowish-gray material, possibly the product of occlusion of a medullary branch of the cortical arterial system; no embolus was found. No similar areas elsewhere. Ventricles contain more than a tablespoonful each of a clear fluid. Choroid plexuses slightly cystiform. Ependyma normal.

Basal ganglia normal and of the usual consistence, except in the middle of the left lenticular nucleus, which presents a stony mass 2 cm. in diameter and slightly flattened from before backward. The mass is closely invested by a thin fibrous capsule and does not shell out. On sawing the middle is found to contain soft opaque grayish material.

Isthmus, bulb and cerebellum normal. Cord: Pia edematous in the middle of the posterior columns of the lower cervical region are small, symmetrical gray areas, suggesting sclerosis. Gray matter everywhere retracts slightly from section surface. On the pia of lower dorsal cord is a single minute white calcified plaque.

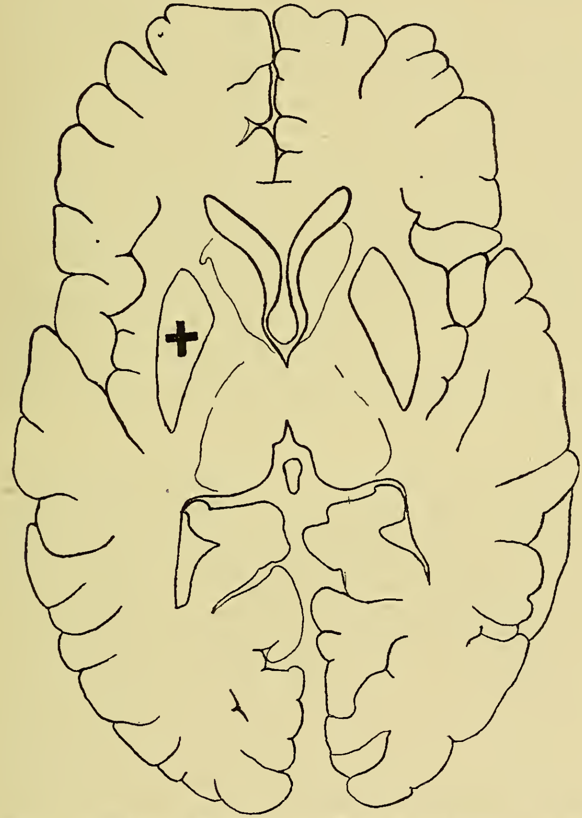

Fig. 1.—Diagram (Dalton, 1885, Series B, Plate vii) to show position of large cholesterin mass.

Microscopic examination of the organs of the trunk showed a slight brown atrophy of the heart muscle, a hemorrhagic infarct in the lung surrounded by a zone of cocci, chronic passive congestion of liver (extreme) and spleen, infarction of the kidney with zone of congestion and leucocyte invasion, an adrenal with high blood content, and a pancreas without notable lesion. There was evidence of arteriosclerosis throughout the organs.

Microscopic examination of the brain and cord showed a moderate subpial gliosis in several places examined. The cortex cerebri, except near the cholesterin masses, was not greatly altered. The tissue of the cord showed very numerous corpora amylacea.

The reaction about the cholesterin masses in the gray matter is slight. A teased specimen from the capsule about the mass in the lenticular nucleus was fixed in formalin and mordanted with picric acid, followed by ammonium bichromate and showed hairlike masses of neuroglia fibrils.

More notable is the reaction about the miliary masses in the white substance of the cord. These foci are grossly evident in sections of the cord fixed in Zenker's fluid, mounted in paraffin, and stained with phosphotungstic acid hematein. The cholesterin masses have become dissolved away; all that remains of a lesion is the cavity surrounded by a narrow zone in which nerve fibers and myelin sheaths are absent and replaced with a fine felt-work of neuroglia fibrils.

Flakes from various masses and from different portions of the large mass in the lenticular nucleus were found to consist chiefly of smaller and larger cholesterin crystals. No tubercle bacilli could be demonstrated among the crystals. One-half gram of material from the middle of the largest mass was injected into the groin of a guinea-pig, but tuberculosis did not follow.

It is not possible at present to give an adequate explanation of this finding. The condition has nothing in common with cholesteatoma, excepting cholesterin, and fails to show the essential element of cholesteatoma, viz., an accumulation of desquamated epidermal cells. It is not possible to prove a relationship of the deposits with the remains of tubercles, of gummata or of multiple abscesses. It is possible that the deposits are related with old lesions of the blood vessels, perhaps with occlusions or with changes in the vessel walls; at any rate, there is unusually widespread arteriosclerosis in the case. Whatever their origin, it is harder to account for their accumulation in solid tissues than in a cavity like the gall bladder.

The chief interest of the deposits must for the present remain in their association with multiple foci of sclerosis. Deposits like those in the cord may readily be overlooked in routine examinations, and the small spaces occupied by the crystals may be taken for artefacts in preparation. A more careful fresh inspection of central nerve tissues, and especially of the cord, may bring out more of such miliary or larger glioses, to which the attention was drawn in the present case only by the presence of large masses in the gray matter of the cerebrum. The case can hardly be unique. With more cases the relationship of the cholesterin with old foci of suppuration or with vascular lesions may be demonstrated.

SUMMARY.

Male of 56 years. General and extensive arteriosclerosis, extending to gross involvement of some secondary branches of the circle of Willis. Death from heart failure. Small masses of pure or almost pure cholesterin crystals in several parts of the cortical and central ganglionic gray matter and in the white matter of the spinal cord. Largest mass, 2 cm. in diameter, in middle of left lenticular nucleus. Thin capsules due to fibrillary overgrowth of neuroglia surround the masses. The relation of cholesterin to miliary glioses in the spinal cord may readily escape attention.

VI

CYSTIC APLASIA OF THE CEREBRAL HEMISPHERES IN AN IDIOT CHILD.*

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(*From the Pathological Laboratory of the Boston City Hospital.*)

The case we here present was one of idiocy in a child which showed an unusual condition of cystic aplasia in the cerebral hemispheres. Some points in the histopathology of the cerebrum, together with developmental modifications in some organs of the trunk, serve to point out a field of work in idiocy

CLINICAL SUMMARY.†

Defective girl, born without the use of instruments in the eighth month, one of twins (the other still-born). Slight evidence of consciousness or orientation. General rigidity. Food given with difficulty. Constipation. Convulsive seizures began after twentieth month. Death in thirty-seventh month.

Gross findings. — The autopsy was performed February 4, 1904 (E. E. S.). A description of the findings in the head, together with a summary of trunk findings, follows:

Head. — Profuse growth of curly, fair hair. Scalp normal. Cranium somewhat abnormal in shape. The occipital bone bulges from the plane of the parietals, as if posterior fossa were relatively larger than the other fossæ. The left posterior quadrant of the vault bulges smoothly from the general surface. There is no evident flattening of cranium in opposite quadrant. Bones can be separated along suture lines with no great violence. Dura tightly adherent to calvarium.

Brain hardened in toto in formalin. Gelatine was injected beneath pia mater of the hemispheres. The cortical wall is thinnest in the posterior halves, and an artificial bulging was produced in the occipital and posterior parietal areas.

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* Received for publication Nov. 5, 1905.

† The full clinical history is given in Med. Surg. Reports of Boston City Hospital, 1905, Article X.

Externally the hemispheres are roughly normal and symmetrical in shape, but fail to show the usual furrows when viewed from above. The brain is almost smooth at both poles when viewed from above, but a tongue of solid tissue with sulcal markings runs from below upwards and backwards in the locus of the central convolutions. From below, the hemispheres are, in general, of a normal appearance. On section the greater portion of the cortex is found to be replaced by wide cystic spaces, freely intercommunicating and traversed by slender lace-like smooth trabeculæ, a few millimeters in diameter. The system of ventricles is independent of the cortical and central cavitation; but the roof of the lateral ventricles is only a few millimeters thick. None of the ventricles is notably dilated.

The cerebellum shows no reduction in size and has the usual markings.

ANATOMICAL DIAGNOSES.

Extensive cystic spaces in upper portion of cerebral hemispheres, best marked near both poles.

Cranial changes, corresponding to cerebral maldevelopment.

Backward muscular development.

Supernumerary spleens.

Malnutrition.

Broncho-pneumonia of right lower lobe.

MICROSCOPIC FINDINGS. — The microscopic work was carried out with a view of getting evidence on the cause and conditions of the maldevelopment. Result was taken to general stains (eosin and methylene blue, the anilin blue stain for connective tissue, and the phosphotungstic acid hematein stain*).

The *organs of the trunk* showed a few points of interest. The immediate cause of death was probably broncho-pneumonia, since foci in the *lung*, 0.5 centimeter or more in diameter, contain an exudate made up almost purely of leucocytes, and there is edema and cell infiltration of many air spaces elsewhere. The bronchial mucosa is as a rule preserved. Near a few bronchi there is a limited amount of lymphoid tissue containing eosinophiles and mast cells. Near the root of the lung there are better defined lymphoid nodules adjacent to plates of cartilage; most of the cells therein have vesicular nuclei and very little cytoplasm, but a few of the cells have nuclei with chromatin murally arranged.

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* F. B. Mallory. A Contribution to the Classification of Tumors. Journ. Med. Research, xiii, 2, January, 1905.

The tissues of the neck were explored for *thymus* tissue, which was found in limited amount and in a few blocks only. The thymus tissue occurs in acini, which are as a rule not over one millimeter in diameter but are now and then drawn out into slender masses 0.5 centimeter long. The acini are surrounded by dense fibrous tissue without cell infiltration. The acini themselves show extensive fibrous change and in places an undue proportion of small vessels. The thymus lymphocytes are few in number by comparison with the larger cells of the connective tissue series. Only a few acini contain thymus pearls. The total amount of thymus tissue found could be contained in an area one centimeter in diameter. The character of the tissue suggests advanced atrophy rather than backward development.

Of the other ductless glands, the *thyroid* was well developed, and showed its secretion largely within the gland spaces. The parathyroids were not found, but no extensive search was made for them. In the *hypophysis* small canals lined with low epithelium were found between the glandular and nervous portions. A few gland spaces contain small plugs of colloid material. The number of eosinophile gland cells is low.

The *spleen* and accessory spleens showed, besides central lesions of the Malpighian bodies probably related to the terminal infection, some peculiarities in the pulp tissue. The most striking feature is the presence of numerous nucleated red blood cells (one or more to an oil immersion field) as a rule of normal size, but often larger than normal. These cells are found both in blood vessels and in the sinuses. The majority of cells in the spleen are a series of cells of various size with vesicular nuclei; these cells are probably derived from endothelial cells lining the pulp spaces. Cells approximating the adult lymphocyte type occur, but are scarcely more frequent than the nucleated red blood cells. The cells of the Malpighian bodies have nuclei rather larger than lymphocyte nuclei, as a rule of a frankly vesicular character, but in some cases assuming a peripheral arrangement of chromatin. These and other features make the spleen difficult of interpretation; there is no evidence of a destructive process for red cells or other cells.

The *heart* showed no lesion except vacuolation of a few fibers.

The *liver* appears normal. The portal veins and the sinusoids of the lobule centers are congested. The liver cells frequently contain numerous small brown or greenish brown granules. The periportal connective tissue is thin but dense, and shows now and then a mast cell.

The *pancreas* and *adrenal* are not remarkable.

The *kidney* shows a degree of development corresponding with that of a child of a year or under.

Brain. — The pia mater is everywhere thin and without lesion. Some of the deep processes which accompany vessels into the interior are considerably broader than is appropriate for the caliber of the vessels. These expanded perivascular spaces contain fluid and many phagocytic cells. The spaces are lined by smooth, abrupt walls of compact neuroglia.

It is often possible to follow along the pial processes till they open out upon the broad cystic spaces which make up a large proportion of the cerebrum. There is no free passage into the interior; both hemispheres held injection perfectly.

The larger cystic spaces are lined by a thin layer of fairly dense fibrous tissue. This fibrous lining becomes expanded in the narrower recesses to contain phagocytic cells. The features of a cyst of softening may be roughly reproduced in a few places. The anilin blue connective tissue stain at once corrects this impression by demonstrating a sudden transition between the compact wall of neuroglia tissue (staining red) and the fibrous wall (staining blue).

The characters of the cyst lining scarcely differentiate it at first glance from the pia mater. The pia mater, however, contains large vessels, and the cyst lining is supplied, as a rule, with capillaries only. Moreover, the pia mater is backed by a cellular neuroglia readily distinguished from the compact neuroglia behind the cyst lining.

Besides the cystic spaces lined with fibrous tissue there is another kind of cyst, small, lined with ependyma, and associated with, or opening into, the ventricles. These cysts were found chiefly adjacent to the posterior cornu, in a site where they occur, as is well known, not infrequently in apparently normal adults. There is no sign that these accessory ependymal cysts dilate extensively, if at all.

The ependymal cysts and the ventricles show cells supplied with long, hair-like processes, which seem to be attached in many cases to basal bodies near the outer surfaces of the cells.

There are occasional gaps in the ependyma lining the ventricle, and adjacent to these the neuroglia cells may be heaped up in small masses. Corresponding with the smaller gaps in the ependyma, the dense subependymal band of neuroglia is demonstrably interrupted and replaced by a looser tissue, in which the more active neuroglia cells, with expanded cell bodies, are found. In some cases the ependymal rupture demonstrably involves the subependymal tissues as well as the line of ependymal cells.

The architecture of the cortical remains is far less familiar in appearance than that of the ventricular region. The narrow strips of tissue which represent considerable stretches of cortex present a regular stratification, such that the peripheral portion is almost constantly more cellular than the underlying or fibrillar stratum. The appearances suggest that the cellular layer corresponds with the cortical gray matter, and the fibrillar layer with the central white tissue or its neuroglia framework.

There is in many places a thin stratum representative of the subpial layer, in which a few fibrils run parallel with the pia. Among these fibrils are a few vesicular nuclei with prominent nucleoli. These nuclei vary in size, but average the diameter of the blood globule with the same fixation. On approaching the larger pial processes the subpial layer of neuroglia gradually thickens, becomes more cellular, and begins to show occasional stouter fibrils. As the layer dips inward along the pial process, it becomes gradually transformed into a less cellular and more fibrillar and compact neuroglia tissue lining the cysts.

There are several variations in the structure of the tissue which represents the cortex. In a given area the structure is fairly regular. The most frequent variation is the appearance of stout bundles of fibers, at regular intervals in the loose intermediary layer of the cortex, running perpendicular to the pia mater. In other places the nuclei accumulate in small foci at regular intervals so that the arrangement of nerve cells in some parts of the normal cortex is imitated.

There is little evidence of gliosis, either cellular or fibrillar, in the sense of the reactive gliosis of adult tissue. In places there is a more dense and compact arrangement of fibrillar masses underneath the cyst lining; if this is reactive gliosis, it is without doubt not recent.

The *cerebellum* shows a normal stratification, numerous Purkinje cells, a molecular layer filled with cell processes, and a granular layer in places thin, but as a rule normal. The vessels, particularly in the dentate nucleus, are dilated. Neuroglia tissue is nowhere prominent; there are occasionally a few coarse fibrils along vessels.

The *medulla* shows a well-developed olive and accessory olives in the levels examined. The pyramidal tracts are lacking, or represented by few fibers. There is no gliosis of the ventral regions. There is very little hint of gliosis elsewhere, except along the upper lateral border.

GENERAL SUMMARY AND REMARKS.

1. An infant, born in the eighth month of pregnancy, one of twins (the other still-born), was backward in development,

gave evidence of extensive nervous defect, with numerous convulsive seizures, and died, when thirty-seven months old, of broncho-pneumonia.

2. The autopsy showed gross cerebral changes. The ground plan of the cerebrum was preserved, but the substance of each hemisphere was largely replaced by a closed cystic cavity, independent of the ventricles. The interiors of the cystic cavities were traversed by delicate strands of neuroglia tissue. The pyramidal tracts failed to develop. The cerebellum had developed almost normally.

3. The nature and time of the original injury cannot be exactly fixed. The agent was probably focal and just severe enough to destroy the nerve cells or nerve cell producing cells, but leave the neuroglia cell-series intact and capable ultimately of producing fibrils. The effect of this differential aplasia is that neuroglia tissue alone serves to maintain much of the ground plan of the cerebral cortex.

4. Although the original injury may have been quite limited in extent, the failure of cell-processes and whole fiber systems to develop coördinately with the expansion of the cerebrum, has increased the ultimate loss of solid tissue many fold.

5. It is probable that the cystic chambers in the cerebrum are in part due to the dilatation of perivascular spaces, with eventual rending apart of their walls, as the brain plan continues to enlarge, and the neuroglia masses contract. There are phagocytic cells in recesses along the fibrous walls of the cystic spaces. It is not clear whether the neuroglia tissue or one of the brain envelopes is the leading tissue in the enlargement of the brain plan.

6. The case showed very little thymus tissue, which was largely overgrown by cells of the connective tissue series. The kidneys were backward in development. There were some peculiarities of the spleen. It is not yet possible to say what part is played herein by the cerebral defect.

DESCRIPTION OF PLATES.

Plates XII., XIII., XIV. Photographs of brain after injection of the cavities in the substance of each hemisphere with formalized gelatin. The irregular bulging of the posterior part of each hemisphere is in part artificial.

Plate XII., Fig. 1, right side; Fig. 2, left side.

Plate XIII., Fig. 3, view from above.

Plate XIII., Fig. 4, and Plate XIV., Figs. 5 and 6. Cross sections showing closed system of ventricles and cystic spaces in substance of hemispheres, with delicate trabeculation. The trabeculæ were found microscopically to consist of columns of neuroglia tissue invested externally with fibrous tissue; the walls of the cystic cavities showed in a few places phagocytic cells.

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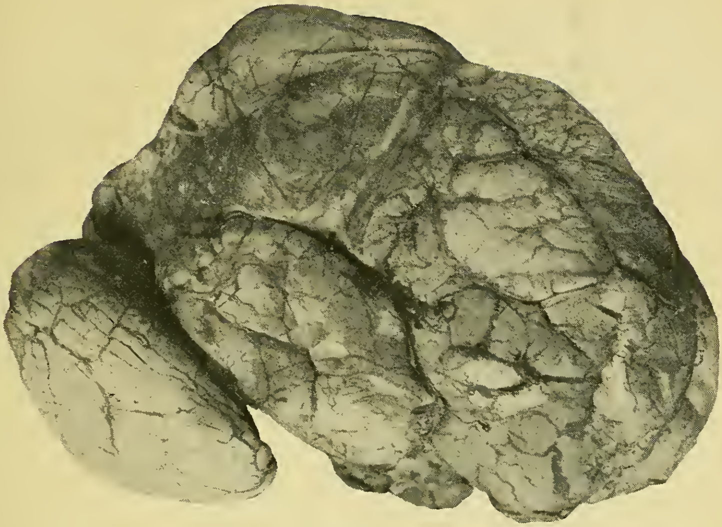

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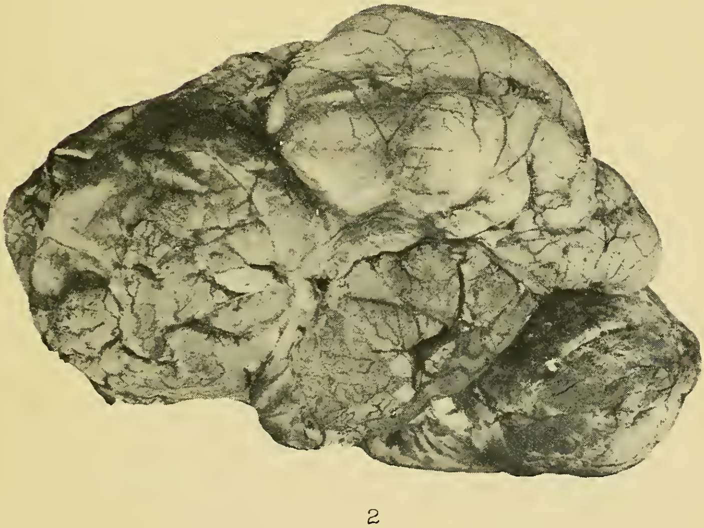

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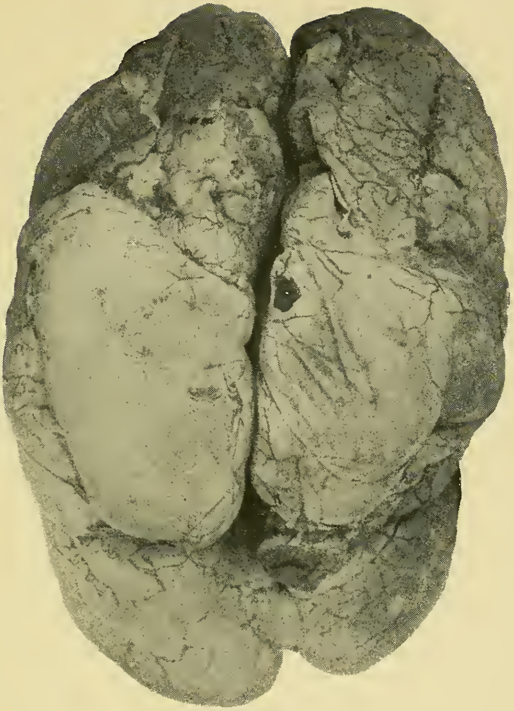

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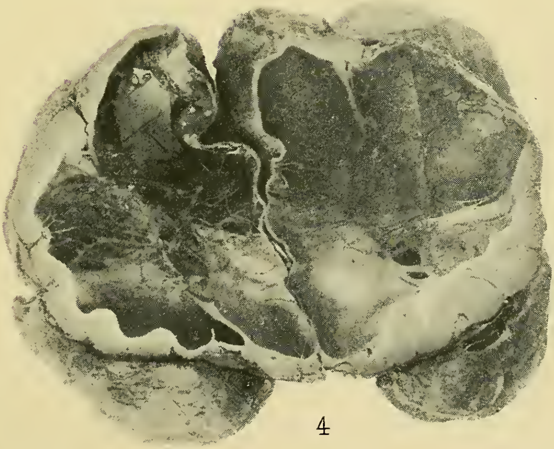

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VII

DIFFUSE GLIOSIS OF THE CEREBRAL WHITE MATTER IN A CHILD.

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The case here reported was that of a child which, after a fall on the back of the head, gradually lost power to walk, grew deaf, dumb, blind, and stupid, and died twelve months after the fall. The autopsy showed a peculiar overgrowth of neuroglia, with some destructive properties, confined to the white matter of the posterior parts of the cerebrum, optic thalami, and areas in the white matter of the cerebellum.

I. CLINICAL HISTORY.

Dr. Bullard.

Edward J., six years old, born in Boston, was first seen January 16. 1904.

There was no history of inheritance. Parents were healthy. There were ten children, patient being the eighth. Of these five were dead, four of "stomach trouble" and one of "meningitis."

The patient had always been well up to the time of the present trouble, except for measles when three years old.

Present trouble: Six months ago while playing in the cellar he fell backward down three steps. He was not unconscious, but got up himself and came up stairs crying. He seems to have had some nose-bleed, and possibly bleeding from one ear. The night following he was feverish and restless, but not apparently delirious. The next day he seemed well, and went out to play as usual. He did, however, have nose-bleed whenever his face was washed.

Since the accident he has been "nervous," and for five months he has had some difficulty in walking, staggering so that he is obliged to put out his hands to steady himself. Has never fallen from this cause. Can use his knife and fork. Mother thinks he is becoming stupid. Frequency of micturition. Is very deaf and has been taken to the Eye and Ear Infirmary, where operation for adenoids was advised.

Physical examination: Same as before, but now he obeys no directions and does not appear to understand or notice what is going on about him. Cries when examined. Walks with very short steps swaying from side to side.

Dr. Holmes (Aural Department) reports: No aural signs to account for the deafness, which is apparently of nerve origin.

July 6. Dr. Williams (Eye Department) reports: Some atrophy of each optic nerve, but not enough to account for almost total lack of vision. The latter is presumably of cerebral origin.

July 13. Was admitted to the Hospital Second Surgical Service, Dr. Monks. Temperature normal. Pulse 100-120.

July 18. Operation. Dr. Monks. Trephined about 1½ inch behind and 1 inch above right ear. Dura thickened. No visible cerebral pulsation. Dura opened. Pia slightly thickened, edematous. Several drachms of clear amber-colored fluid drawn from lateral ventricle.

July 20. Died.

II. ANATOMICAL FINDINGS.

Permission was granted to open the cranial cavity. The examination was made fifteen hours after death by Dr. R. L. Thompson, whom we wish to thank for his record. The child was 129 cm. long. Development fair. Nutrition good. Pupils equal, 5 mm. wide. Circumference of skull 53 cm. Frontal suture well marked. Surgical opening 1 cm. square in squamous portion of right temporal bone, 5 cm. above and behind external auditory meatus. Dura everywhere adherent to calvarium.

Brain with pia mater weighs 1,445 gms. Pia mater and vessels normal. Convolutions symmetrical. Substance very firm toward occiput. Ventricles contain a normal amount of fluid tinged with blood. Cruor clot, 2 cm. in diameter, in descending horn of right ventricle.

The white matter of the posterior part of the centrum semiovale in both hemispheres is replaced with grayish or straw-colored slightly translucent material of a dense consistence. The lesion is somewhat sharply limited to the white matter; the cortex, of a paler color, sinks below the surface of section. In the right occipital region there is a narrow layer of less dense white matter between cortex and lesion.

The areas of increased density were roughly marked out at autopsy. On the right the lesion involves and in part replaces the white matter of the occipital, parietal, and temporal lobes. The right optic thalamus is somewhat firmer than normal. In the left hemisphere the lesion is still more marked and almost everywhere replaces the white matter of the occipital, parietal and temporal lobes. The left optic thalamus is even firmer than the right. The lesion on the left side stretches at least 1 cm. anterior to a frontal plane taken just in front of optic thalamus. Pieces were removed for fixation in Zenker's fluid, and the rest of the brain was hardened in 10 per cent. formaldehyde.

III. MICROSCOPIC FINDINGS.

The sclerosis of the cerebral substance preserves on microscopic examination the same remarkable limitation to the central white matter which was noted in the gross. Except in the optic thalami, the limits of the white matter are nowhere transgressed by the neuroglia overgrowth. The exterior of the lesion in some parts of the occipital region follows the contour, and coincides precisely with the inner limits of gray matter. But, in general, the sclerosis corresponds rather to the body of white matter known as the centrum semiovale and may spare the intragyral portion of the white matter.

In spite of the massive character of the lesion, and the compactness of many portions of its structure, the overlying cortex fails to show major lesions, such as secondary changes in nerve cells due to the loss of their processes, or accumulations of phagocytic cells in vessel sheaths, or a reaction on the part of the neuroglia. It is noteworthy that even the upper or subpial layer fails to show a reaction on the part of the neuroglia, despite the frequency of this reaction under numerous conditions. The pia mater and its vessels are likewise free from lesion.

The extent and nature of the damage done by the lesion cannot be exactly determined. The volume of brain tissue remains unaltered or has been slightly increased by the lesion. There has been at some time considerable destruction or alteration of tissue in the region, as is shown by dense deep masses of pigment-bearing phagocytic cells in the sheaths of the appertaining vessels. The myelin sheaths, and doubtless numerous axis cylinders, have been destroyed in the area of sclerosis. In certain areas which seem paved with neuroglia giant cells separted by a few delicate neuroglia fibrils, it is certain that the original elements must have been destroyed.

In other parts it is by no means certain that all or even the majority of the axis cylinders have been dissolved in the lesion. In a preparation stained with phosphotungstic acid hematein (Mallory) it is possible to follow certain myelinated fibers, in whose myelin sheaths a delicate skeletal substance may stain, till the fibers enter the sclerotic area and lose their myelin. Neither myelin nor the delicate substance within the sheath can be demonstrated in quantity within the sclerotic area.

The anilin blue stain (Mallory) for connective tissue is of service on this point. It is possible for instance, to demonstrate in this case, by means of the anilin blue stain, the secondary degeneration of fiber bundles about the Gasserian ganglion and the secondary degeneration of most of the central bundles of the optic nerve. Unfortunately the application of the anilin blue stain to the brain substance of this case is of less service. For it proves not possible to differentiate convincingly the supposed axis-cylinders from long cell processes of some of the large active neuroglia cells which characterize many parts of the sclerotic regions. However, so far as appearance without differential staining can convince, it is possible to say that at least some axis cylinders, minus myelin, penetrate the sclerotic areas. This would align the case with the cases known as multiple sclerosis.

The finer characters of the lesion are of interest, especially as bearing on the differentiation of gliosis from glioma.

The sclerotic tissue varies strikingly in microscopic structure, although the amount of intercellular substance is everywhere above that of the normal cerebral white matter. The variations are chiefly shown in the number and character of the neuroglia cells which produce the fibrils. The transitions in the mass of the lesion are never abrupt and never so well marked as the transition between the sclerotic tissue and the relatively normal cortex. The neuroglia cells vary in number and size in the sclerotic tissue, just as they do in those focal overgrowths of neuroglia tissue which we know as gliomata.

In places (characteristically along the exterior of the sclerotic tissue), the cells are small, placed at fairly regular intervals, and provided with branched cell-bodies which somewhat recall the characteristic cell bodies of reacting sub-pial neuroglia cells.

In other places (characteristically in the interior of the lesion), the cells are larger (often meriting the name giant cell), placed at smaller intervals (sometimes giving a pavemented appearance to the lesion), and provided with numerous overlapping nuclei which are crowded about the periphery of the cell. The centers of these large cells are homogeneous and finely granular and are provided with a varying number of centrosome-like structures.

In a few foci, there is a third type of cell in which activity seems to be spent on expansion of the cell-body and the production of numerous heavy, branched, and deeply staining processes, which are sometimes frayed at the ends like cut wire-rope.

In places there are remarkable clusters and rows of ependymal cysts, lined with perfectly formed ependymal cells, which are provided with basal bodies and attached cilium-like appendages. These cysts are not of diffuse occurrence but occur particularly in the neighborhood of the posterior horns of the ventricles. Occasionally the cysts are so aligned, between stratified masses of neuroglia coincident in direction with the major axis of the ventricle, that the impression is gained that such accessory cystic spaces are developed along with the ventricle and belong to its ground plan.

Over against these perfectly formed ependymal cysts may be set certain less regular cysts which are perhaps due to the hollowing out of the cytoplasm of some of the giant cells with peripheral nuclei noted above. Such irregular cystic spaces are, however, not common in this tissue.

The gradual variations in cell character above noted, taken together with certain variations in the amount and texture of the intercellular fibrillary substance (often particularly dense about vessels), are not inconsistent with the diagnosis, glioma. There is considerable evidence of tissue destruction throughout the sclerotic tissue in the shape of dense deep masses of pigment-bearing phagocytic cells in the vessel sheaths. The material so laid down is probably derived from the destruction of nerve fibre constituents incident to the lesion, since there is nowhere any sign of necrosis in the sclerotic tissue itself and there is little or no accumulation of phagocytic cells in the overlying cortex or in the pia mater.

IV. SUMMARY.

1. Boy of six and a half years. Measles at three years. One year before death, fell backward down three steps in a cellar, with epistaxis, and possibly bleeding from ear. Afterward "nervous." A month later began to stagger in walking, became gradually deaf and stupid, later blind and dumb. Operation for chronic internal hydrocephalus. Death two days after operation.

2. The autopsy showed sclerosis of the white matter of the occipital, parietal, and temporal lobes on both sides with sclerosis of optic thalami and of small, roughly symmetrical areas in the white matter of the cerebellum.

3. The microscopic examination shows a cellular and fibrillary overgrowth of neuroglia, sharply limited to the white matter. The picture gradually varies from that of masses containing giant cells and few fibrils to that of active fibril-producing cell masses or that of stratified areas of inactive fibrillar gliosis.

4. The lesion involves the destruction of myelin sheaths and considerable axis-cylinder material. The lesion may be described as a multiform gliosis of the white matter with extensive mildly destructive properties. The nutrition of the areas is maintained. The overgrowth of neuroglia substitutes for, and to some extent destroys, the involved tissues, but fails to invade, in the sense of invasion by glioma. The overlying cortex fails to show important changes. The origin of the condition is unknown.

VIII

CEREBRAL SEIZURES WITH SUBOCCIPITAL PAIN: MILIARY CEREBRAL AND GROSS VERTEBRAL ANEURYSMS.*

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THE following case suggests the difficulty of diagnosis in cranial conditions anatomically simple. A woman of sixty-nine years presented a series of cerebral seizures without focal signs, leading to fatal issue in nineteen days. The seizures were ushered in by boring suboccipital pain. The autopsy revealed several successive voluminous hemorrhages so situated in various parts of the cerebrum that the fibres of the projection system were largely spared. The small cerebral arteries, both of the cortical and the ganglionic systems, were beset with miliary aneurysms. Both vertebral arteries opposite the junction of bulb and cord, showed gross aneurysmal dilatation.

I. *Clinical History.* — Widow of sixty-nine years. For a year before her last illness she showed a tendency to drowsiness in the daytime and would even fall asleep in company.

She was taken one evening, nineteen days before her death, with sudden, severe, suboccipital pain, described as boring and confined to a spot the size of a fifty-cent piece. The pain was at first attributed to neck strain, produced by gazing up at mural paintings the afternoon of the attack. The pain was followed shortly by projectile vomiting with retching. These symptoms persisted for two days. The day after the attack the pain became less severe and changed to a dull ache, constant in the original situation and varying in intensity, without, however, relation to movement or position of the head and neck. On the fourth and fifth days of the illness there were slight chills with sweating. Evening rise of temperature from 1° to 3° F.

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* Read Feb. 15, 1905, at a meeting of the Boston Society of Psychiatry and Neurology.

Examined Nov. 1, 1905 (W. D. R.). Development good. Considerable adipose tissue. Mind clear. Attitude cheerful. Eyes: Movements normal; pupils react readily to light and distance. Head: No tender spots; no bruit heard; no rigidity or retraction of neck; no inequality in sides of face; no paralysis of facial muscles. Tongue: Protruded straight, dry, coated, cleaning in center. Breath foul. Throat: Negative. Pulses: Regular, 68, of good volume with increased tension. Moderate degree of radial and brachial arteriosclerosis. Heart: Right border two finger breadths to right of right edge of sternum; upper border at third rib; left border in nipple line; apex in fifth space in nipple line; action regular; sounds of good intensity; systolic blowing murmur over aortic orifice; aortic second sound accentuated. Lungs: Negative, except for a few moist râles in both bases behind. Abdomen: Negative. Spleen: Not felt. Extremities: Normal. Reflexes: Superficial reflexes slow; knee jerks slow and equal; Kernig's sign absent; Babinski's sign absent. Leucocytes, 17,000.

The evening of Nov. 2 (eighth day of illness) came another attack of boring pain, localized as before, lasting eight or ten minutes. The mind wandered during the attack. There was steady improvement. The temperature remained slightly elevated. The pulse ranged from 60 to 68. The mind was clear. The attitude cheerful. The dull aching pain continued in the back of the head.

The morning of Nov. 13, after passing a comfortable night, the patient complained of a sudden cold feeling in the forehead. Consciousness became clouded. Coma and Cheyne-Stokes breathing set in with death in about two hours.

Clinical Summary. — Woman of sixty-nine, with moderate arteriosclerosis and an enlarged heart. Attacks of severe, boring pain, localized in an area the size of a fifty-cent piece, in the suboccipital region (first and eighth days). Slight chills (fourth and fifth days). Temperature slightly elevated with morning remissions. Leucocytes, 17,000. Death in coma two hours after a sudden cold feeling in the forehead (nineteenth day).

II. *Autopsy Findings* (E. E. S.) — Well developed woman of middle height. Nutrition good. No edema. Pupils equal, not dilated.

Trunk: Subcutaneous fat of abdomen 5 cm. deep; cavities normal; mesentery very fatty; mesenteric lymph nodes not palpable.

Heart: Considerable epicardial fat; heart much enlarged; valves normal, except for raised yellow areas of sclerosis in mitral leaflet; muscle of both ventricles unusually firm and without opacities; right ventricle 1 cm., left ventricle, 2.5 cm. thick; chambers contain freshly clotted and liquid blood; coronary arteries show nodular sclerosis. Lungs: Normal; post-mortem congestion of bases beginning; slight superficial fibrous thickenings at each apex; bronchial lymph nodes not remarkable. Spleen: 18 cm. long; capsule smooth and slightly thicker than usual; substance firm, not pulpy; Malpighian bodies made out; trabeculæ slightly increased; splenic artery shows marked stiffening. Liver: Chestnut brown, firm; lobulation made out with difficulty. Gall bladder: Small, buried in smooth old adhesions; contains no stones. Pancreas: Normal. Gastro-intestinal tract: Normal on inspection and palpation. Kidneys: Strip readily, leaving a roughened surface; numerous small cysts over anterior surfaces of both kidneys; pea-sized aberrant adrenal, 2 cm. from hilum, midway between poles imbedded in anterior surface of right kidney; substance shows opacities suggesting fat. Pelves normal. Adrenals normal. Genitalia: Atrophic.

Head: Hair fairly thick and streaked with gray. Scalp: Strips readily. Calvarium: Thick (in places 1 cm.) and dense. Dura: Tightly adherent to calvarium over all, but inseparably adherent to occipital bone. Sinuses: Normal. Arachnoidal villi: Slightly developed. Pia mater: Everywhere reddened by hemorrhage or dissolved blood pigment. The frank areas of hemorrhage involve the sulci of the anterior and mesial surfaces of the cortex cerebri in the area of distribution of the anterior cerebral arteries. The flanks and posterior pole of the brain show reddening, and congestion of superficial sulcal veins, but no fine injection. Over the sulcal veins of the vertex are slender streaks of fibrous thickening. Vessels: At base show diffuse and nodular sclerosis. Both vertebral arteries show fusiform aneurysmal dilatations, 0.75 cm. in diameter. The circle of Willis is apparently pervious. The primary branches of the middle cerebral arteries show nodular sclerosis in patches 0.5 to 1 cm. long.

Substance. — Convolutions flattened. Anterior pole of left hemisphere contains a core of clotted blood and tissue detritus occupying the centrum semiovale under the first and second frontal gyri. The clot is fresh and can be readily turned out from its bed above the forceps minor. The upper fibers of the forceps minor and anterior quarter of the tapetum have been destroyed by the hemorrhage and show a moist, ragged, grayish surface. The hemorrhage approaches the surface in the gyrus rectus and about the olfactory lobes; thence the blood has oozed into the orbital and polar sulci.

A similar hemorrhage fills the white matter of the right anterior pole above the forceps minor, but has broken down the gray matter at the pole. The clots on the right side cannot be turned out so readily as those on the left. Small vessels with tightly adherent small masses of mixed gray and red clot are demonstrable in the bed of the hemorrhagic area. Fresh oozing into the cortical sulci has occurred on the right side as on the left. The ventricles contain no blood and no increase of fluid. Ependyma normal. Posterior parts of lateral choroid plexuses cystic. Basal ganglia, inter-brain, isthmus, cerebellum normal.

Pituitary surrounded by effused blood.

Blood serum cultures from hemorrhage into right frontal lobe and from right basal ganglion remained sterile.

The pia mater and vessels were macerated out in running water by Mr. J. B. Ayer, and both the cortical and the ganglionic systems of arteries proved to show in their smaller branches numerous miliary aneurysms. These were sometimes saccular, sometimes fusiform in shape.

Anatomical Summary. — General arteriosclerosis (aortic, coronary, cerebral, splenic, renal). Fusiform aneurysms of both vertebral arteries. Miliary aneurysms of cortical and ganglionic arterial systems.

Extensive multiple cerebral hemorrhages (of varying age) in substance of anterior poles of brain and elsewhere, with oozing into superficial pia mater.

Hypertrophy of heart, endocardial sclerosis, arteriosclerotic nephritis, apical scars of lungs, chronic pericholecystitis, chronic adhesive external pachymeningitis, chronic fibrous leptomeningitis, aberrant adrenal in right kidney.

III. *Microscopic Findings.*— The microscopic examination was chiefly confirmatory of the gross findings. The organs of the trunk showed relatively more arteriosclerosis than the intracranial tissues. The kidney showed numerous advanced chronic changes with extensive arteriosclerosis, numerous atrophied glomeruli and tube-casts. The lungs showed no signs of acute inflammation. The spleen showed numerous hemorrhages into the pulp and a heavier framework than usual, but failed to show acute alterations.

Numerous sections were made from the cerebrum, medulla and cord. The cerebral hemorrhages proved to be distinguishable into fresh hemorrhages, hemorrhages with numerous phagocytes containing unaltered blood globules, and hemorrhages containing pigment-phagocytes. Of the fresh hemorrhages, many were small dissecting hemorrhages about the smallest vessels; but very few of these vessels showed demonstrable ectasia or alteration in the elastica. The older areas exhibited numerous phagocytic cells inclosing blood globules, sometimes in scores. The most numerous phagocytes occur in the sulci in the neighborhood of the larger vessels. The pigment-phagocytes are generally distributed and have often lost their spherical shape. There are strikingly few signs of cellular exudation anywhere in the meninges, although an occasional large sulcal vein will show a minute collection of cells of the lymphocyte series at a single focus in the adventitia. Signs of reaction on the part of the nerve tissue are few. There is an occasional strip of the outer cortical layer, which shows a number of swollen neuroglia cells; but these are enmeshed among rather dense fibrils, and there is evidence of a general but focally varying superficial fibrillar gliosis, probably long antedating the hemorrhages and still condensing. The pyramidal nerve cells show considerable over-pigmentation.

Similarly in the region of the vertebral aneurysms the diffuse gliotic alteration of the superficial zone and in the neighborhood of the posterior roots is part and parcel of a more general process, exhibited equally in the medulla beyond the zone of immediate aneurysmal pressure. Nevertheless, we cannot exclude this gliosis from influencing in some degree the regionary pain. The vessels of the cord and medulla themselves show little alteration. There was no convincing evidence of alteration in the nerve bundles in the walls of the vertebral aneurysms. Slender collections of cells of the lymphocyte series lie in the connective tissues opposite the middle of the walls of the aneurysms, where breaks in the elastica and thinning out with occasional fenestration of the muscular layer occur.

IV. *Remarks.* — Aneurysms of the vertebral arteries, like those of the other cerebral arteries, are rarely made out in life and are usually discovered by medical examiners in cases of sudden death. v. Hofmann, 1894, mentions ten cases of aneurysm of vertebral artery with fatal rupture, over against twenty cases of Sylvian, thirteen cases of carotid, and ten cases of basilar aneurysm in the same series.[1] Curiously enough, the youngest victims of basal aneurysm in v. Hofmann's series showed left vertebral aneurysm (a girl of ten dying suddenly in convulsions, and a boy of fourteen dying suddenly). From time to time, however, cases of vertebral aneurysm without rupture and with definite symptoms have been reported. As examples of these and for comparison with our own case, we have abstracted in particular the irritative case of F. Schultze, 1875, the slowly destructive case of Ladame and Monakow, 1900, and the case with fatal rupture of Rindfleisch, 1905.

F. Schultze, 1875, reported a case of aneurysm the size of a cherry in the left vertebral artery about one-half inch from the junction with the basilar artery, so placed as to compress the left seventh and eighth nerve roots.[2] The subject was fifty-six years old and died of phthisis, showing no effects of the aneurysm save a pronounced *tic convulsif*. The tic had lasted about a year, and consisted in brief, rapidly recurring clonic contractions of the left side of the face, starting up or augmenting with speech or mastication. The intervals without tic varied. The frontalis, ear muscles and palate were not involved. Pain was absent. There were no points of pressure by which to evoke the contractions.

Ladame and Monakow, 1900, reported a case of aneurysm of the left vertebral artery in a man of sixty-eight, with a history of syphilitic infection at thirty.[3] The symptoms began about two years before death with vertigo and attacks of angina pectoris. After a particularly violent apoplectiform attack, a cerebellar gait developed, with dysarthria, some dyspnea, cerebellar agraphia, and occasional pains in the left arm. After six months of such symptoms, the patient had a violent seizure with vertigo and vomiting but without loss of consciousness. Thenceforward the patient always fell to the left, would no longer walk, stand or sit up, and showed loss of pain and temperature sense on the right side of the body, left abducens palsy, slight left ptosis, and narrowed left pupil. Swallowing became difficult, stupor and coma followed, with death two years after onset of earliest symptoms, forty days after the last seizure. The autopsy showed an aneurysm the size of a pigeon's egg of the left vertebral artery near its junction with the basilar artery. There was corresponding atrophy of the pons, cerebellum, olive, pyramid, and left acoustic nerve, with slight atrophy of the left fifth, sixth, ninth and tenth nerves.

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[1] v. Hofmann: Ueber Aneurysmen der Basalarterien und deren Ruptur als Ursache des plötzlichen Todes. Wiener Klinische Wochenschr., November, 1894.

[2] F. Schultze: Linksseitiger Facialiskrampf in Folge eines Aneurysma der arteria vertebralis sinistra. Virchow's Archiv., Bd. 65, H. 3, 1875.

Rindfleisch, 1905, reports a case of aneurysm of the right vertebral artery, with fatal rupture, in a woman of fifty-one.[4] For ten years she had had attacks of asthma and edema of the legs. For three years she had had eructations and headaches. Three days before entrance to the hospital she had been taken with sudden eructations and pains in the back of the head. On the day of admission she had two attacks of stupor with facial cyanosis, transient Cheyne-Stokes breathing, and râles in the lungs. The first attack began with a feeling of terror and screams. In both attacks the corneal and patellar reflexes were lost. The pupils were narrow and reacted to light.

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[3] Ladame et Monakow: Aneurysme de l'artère vertebrale gauche. Nouvelle Iconographie de la Salpetrière, Tom xiii, 1900.

[4] Rindfleisch: Zur Kenntnis der Aneurysmen der basalen Hirnarterien und der bei den intrameningealen Apoplexien auftretenden Veränderungen der Cerebrospinalflüssigkeit. Lichtheim's Festschrift. Deutsches Archiv f. klin. Medizin, Bd. 86, Heft 1–3, 1905.

On admission were noted subfebrile temperature, slight edema of the legs, moderate facial cyanosis, diffuse râles in the lungs, weak skin reflexes and weak normal plantar reflex, absent abdominal, patellar and Achilles reflexes and hemorrhages in the fundi. Coma set in shortly, with slowed pulse, increased cyanosis and deep, noisy breathing. The patient improved with artificial respiration, but remained drowsy. Lumbar puncture yielded fluid containing considerable blood, which failed to clot. Death followed on the third day after admission to the hospital in coma, with cyanosis and cessation of breathing while the heart remained beating.

The autopsy showed all the fossæ at the base of the brain filled with blood. The clots overlay the medulla oblongata, pons and chiasma. The blood was derived from the rupture of a bean-sized aneurysm situated on the mesial side of the right vertebral artery about 0.5 cm. before the junction of the two vertebral arteries.

The earlier literature of vertebral aneurysms is given by Lebert, 1866.[5] No case like the present appears to have been recorded, although Gray's "Anatomy," under the heading of "Surgical Anatomy of the Vertebral Arteries," refers to a case of Drs. Ramskill and Bright, in which regionary pain was due to disease of this artery.

Our own case may be classified as irritative. It is probable that the striking attacks of suboccipital pain were brought on by a combination of factors, through pressure of the vertebral aneurysms, aided by heightened intracranial pressure attending the cerebral hemorrhages. The chronic alterations of the cord and posterior root areas were no more marked than the chronic alterations above and below the region of the vertebral aneurysms; yet it is possible that the spinal gliosis found may be related in some way with the attacks. Attention may also be called to the dense pachymeningitis of the posterior cranial fossa. A closer study of non-destructive lesions would be desirable in such cases.

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[5] Lebert: Berliner klin. Wochenschr., 1866.

Pain in the back of the neck (*regio nuchæ* of His) is a symptom of some interest. Over and above a number of obvious causes, such as local inflammation of the skin, the muscles and the supportive tissues, cervical caries and osteomyelitis, pachymeningitis, leptomeningitis, neoplasms and various agents of local compression of peripheral nerves of the upper cervical segments, there are a number of obscure conditions of nuchal pain and particularly of pain in the middle of this region (*fovea nuchæ* of His). Special names are often reserved for the fixed or relatively permanent neuralgia of this region, as cervico-occipital neuralgia, occipitodynia. Occipitodynia in a certain context of symptoms is accepted as a sign of neurasthenia. Occipitodynia figures prominently in the well-known diagrams of referred pain in visceral disturbance, often under the caption "spinal irritation."

The search for the particular cause of a given pain is not always as minute as it might be. Pains are, perhaps, too readily classed as functional. The orthopedists occasionally insist on the possible relation of neuralgia to the pressure of dilated or varicose veins upon the regionary nerves. The present case brings out the possibility that arterial disease may effect the same result in one of the favorite sites for functional pain.

The puzzling features of this case of cerebral seizures with coma, ushered in by suboccipital pain, appear to be reasonably accounted for by the post-mortem findings: numerous successive hemorrhages into the silent areas of a cerebrum showing numerous miliary aneurysms, and gross aneurysms of both vertebral arteries opposite the junction of bulb and cord.

IX

A Study of Acute Leptomeningitis (Streptococcus Pyogenes.)

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BOSTON.

A STUDY OF ACUTE LEPTOMENINGITIS (*STREPTOCOCCUS PYOGENES*).*

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The present report comprises a series of human brain infections with *Streptococcus pyogenes,* together with the results of experimental inoculation of streptococci in the brains of guinea-pigs. The human cases have been studied histologically with particular reference to, first, the age of the exudations; secondly, certain prominent vascular lesions; thirdly, the neuroglia reaction. The guinea-pig tissues are of value mainly in the study of the exudation. The work has been carried on with methods like those employed in two previous studies, on infections with *Staphylococcus pyogenes aureus*[1] and with pneumococcus.[2]

We have little evidence to bring on the vexed question of the relationship of pneumococcus and streptococcus. The lesions reported here differ in no constant feature from those reported by Southard and Keene in 1905 for the pneumococcus.[2] The effects of the two organisms on tissues, so far as observable by the methods used, would place the organisms in one group.

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*From the pathologic laboratories of the Boston City and the Danvers Insane Hospitals.

* Read in the Section on Pathology and Physiology of the American Medical Association, at the Fifty-seventh Annual Session, June, 1906.

[1] Southard, E. E., and Keene, C. W.: "A Study of Acute Hemorrhagic Encephalitis (*Staphylococcus pyogenes aureus*)," Am. Jour. Med. Sci., March, 1905.

[2] Southard, E. E., and Keene, C. W.: "A Study of Brain Infections with the Pneumococcus," THE JOURNAL, vol. xlvi, Jan. 6, 1906, p. 13.

We are under obligations to Professors Councilman and Mallory for direction of the work, to the various members of the City Hospital and the Danvers Insane Hospital staffs, named below, for the clinical sketches, to Dr. E. E. Tyzzer for his private case, and in particular to Drs. C. W. Duval and P. A. Lewis for supplying us with cultures in the course of their pneumococcus work in 1904-5.[3]

CASE 1.—G. K., male, aged 35, was admitted to Dr. J. Orne Green's aural service at the Boston City Hospital, March 31, 1900.

Clinical History.—Patient had had four attacks of chills and fever in past two years. Two weeks before admission there had been headache, malaise, severe pain in both ears, followed by bloody discharge two days later, and by a chill two days later. Pain in vertex of skull a little to right of median line, restlessness, insomnia, vomiting. Night before entrance, rigor for five minutes, followed by sweating, temperature 104. Both tympana were found perforated and remains of drum swollen. Tongue was coated and tremulous. Temperature rose to 103 and 105 and remained high during the day following. Leucocytes 16,000, April 5. Mastoid exploration: *Streptococcus pyogenes*. Improvement in headache, temperature 103. April 8, temperature 105.5, leucocytes 8,000. April 10, delirium, dilatation of pupils, vomiting, hiccough. April 11, muttering delirium, almost constant hiccough, fixed and dilated pupils, fibrillary tremor of neck and arm muscles, retraction and rigidity of neck. Death, April 12. Arms rigid four hours before death.

Autopsy Findings.—The autopsy, performed 10 hours after death by Dr. Fulton, gave the following head findings, with abstract of trunk findings: Calvarium normal. Sinuses normal. Dura slightly more tense than normal. Subdural space dry. Convolutions flattened. Scattered over the cortex are a few small yellowish opaque areas (2 to 3 mm. in diameter) set, as a rule, along blood vessels of the sulci. The material in these areas is tough and tenacious. The largest area (about 1 cm. in diameter) is on the mesial surface of the left frontal lobe. Yellowish-white fibrinopurulent exudate covers optic chiasm, optic tracts near chiasm, the cranial nerves, the under surface of pons and medulla, the superior vermis of the cerebellum. The exudate does not communicate with the auditory meatus. The ventricles contain from 30 to 50 c.c. of cloudy gray fluid and a small amount of pus in each posterior cornu. Choroid plexus is swollen and grayish. There is pus in lateral recesses of fourth ventricle. Mastoid operation in right ear. Left middle ear contains a slight amount of serous fluid.

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[3] Duval, C. W., and Lewis, P. A.: "Studies on the Pneumococcus," Jour. Exper. Med., vol. vii, No. 5, August, 1905.

Anatomic Diagnosis.—Acute leptomeningitis, encephalitis, and ependymitis. Mastoid operation (right side). Acute splenic tumor. Decubitus of right buttock. Echinococcus cyst of liver. Slight endaortitis. Chronic fibrous pleuritis.

Microscopic Findings.—Cultures from cortex, optic nerve, ventricles and lung gave *Streptococcus pyogenes.* Cultures from heart, spleen and liver were sterile, from kidney negative.

The cortex shows a deep meningeal exudate in which the phagocytic cells far outnumber the other types. The distribution of cells is irregular, since in a few foci about veins there are dense groups of lymphocytes. In a very few places there are fields with polynuclear leucocytes predominating. Vascular lesions are not prominent. The cortical tissue shows little evidence of lesion other than a swelling of the neuroglia cell bodies of the subpial layer. There is no evidence of multiplication of these cells.

The acute inflammation of the lining of the ventricle is shown by a diffuse infiltration with polynuclear leucocytes and an almost universal diffuse swelling of neuroglia cell bodies. The ependyma appears in places as a double or triple row of irregularly arranged cells. Among the ependymal cells is an occasional leucocyte.

The choroid plexus shows an exudate both within and between the folds. Connective tissue cells about the vessels within the folds are swollen. In places there is a dissection of the epithelial cells away from central fibrous tissue by means of polynuclear leucocytes. The vacuoles of the epithelial cells are often perfectly demonstrated, even in folds packed with leucocytes. Of the cells outside the epithelium, the majority are polynuclear leucocytes, mixed with desquamated epithelial cells and a limited number of cells of the phagocytic series. There are few cells of the lymphocyte series.

The cord shows a meningeal exudate in which polynuclear leucocytes are still numerous, but are outnumbered both by phagocytic cells and by cells of the lymphocyte series. In some places the lymphocytes exceeded the phagocytic cells in number. Cells of the plasma cell type stand out prominently, especially when they contain two or three nuclei. The phagocytic cells contain both fat and exudative cells. Of the included cells, lymphocytes and plasma cells are the most prominent; but polynuclear cells are also seen; and it was not rare to find cells of all three kinds engulfed in a single phagocyte. Some of the plasma cells escape inclusion and undergo a spongy vacuolation of the cell-body, which remains basophilic very late, together with a swelling of nucleus and clumping of chromatin.

At the points of deepest exudate the vessels have undergone extensive local lesions. All three coats of the arteries may be involved; the adventitia shares in the general meningeal exudate, emigrating leucocytes may be found sometimes in the muscularis, and the intima is often lifted by exudate cells. There are more polynuclear cells and deposits of fibrin about the arterial lesions than elsewhere. In the walls of the veins polynuclear cells and particularly plasma cells are prominent.

Case 2.—J. D., male, aged 49, was admitted to Dr. J. Orne Green's aural service at the Boston City Hospital, May 30, 1900.

Clinical History.—Patient had had pneumonia at 30. There had been severe headache and a discharge from right ear for three weeks. On admission ear showed slight infiltration of membrana tympani and looked convalescent. There was drowsiness and severe headache. Heart was enlarged to left. Arteriosclerosis. May 31, pain also in back and hips, increasing stupor, followed by unconsciousness at noon. Retention. Bloody urine drawn by catheter. Death, June 1, in coma with slight rigidity of extremities and moderate dilatation of pupils.

Autopsy Findings.—The autopsy, performed 54 hours after death by Dr. H. C. Low, gave the following head findings, including an abstract of the trunk findings:

Dura is only slightly adherent to calvarium. Vessels of dura are considerably injected. There is no sign of thrombus in any of the sinuses and no edema. Vessels of pia are considerably injected. There are few slight subpial hemorrhages over vertex. Near vertex, more especially near the posterior part, there is a fair amount of purulent secretion, and over the top of the cerebellum, between the posterior parts of the hemispheres and over nearly the whole of the base of the brain, there is considerable thick purulent exudation. On the under side of the right temporal lobe is a small place nearly 1 cm. in area where the cortex and meninges are adherent to the base of the skull. At this point a little pus came from the brain tissue. On cross section through both hemispheres at this point there is exposed in the right temporal lobe an abscess cavity about 3 x 3 x 4 cm. This is filled with thick yellow pus. About this for an area of from 1 to 2 cm. the brain tissue is soft and reddish and numerous dark red points fill nearly the whole of the rest of this lobe. No other abscesses are found in the brain tissue. In the ventricles there is a fair amount of thick purulent secretion which covers the choroid plexus.

Both middle ears are normal. The point where the brain and meninges are adherent to the skull is near the center of the right middle fossa just anterior to the eminence of the semicircular canals, and on chiseling away the bone from here, pus is found to be in some of the bone spaces. Just posterior to this, but a little more to the side, for nearly over the entire end of the external canal there is a slight amount of pus in the bone spaces. Mastoid cells have been scraped out in operation. Mastoid cells anterior to field of operation do not appear to be subject to any suppurative process.

Anatomic Diagnoses.—Acute leptomeningitis and ependymitis. Abscess of right temporal lobe. Suppurative osteitis of petrous portion of right temporal bone. Mastoid operation. Acute hemorrhagic cystitis. Healed pulmonary tuberculosis with localized tuberculous pleuritis. Chronic fibrous pleuritis. Slight chronic interstitial nephritis. Hypertrophy and dilatation of heart. Slight area of fatty change in mitral valve.

Microscopic Findings.—Culture from lateral ventricle gave *Streptococcus pyogenes.* The brain abscess contained a variety of organisms. Cultures from heart's blood, spleen, liver and kidney were sterile.

The histologic changes in the cortex are chiefly related to the underlying abscess. The meningeal exudate is slight and composed of mononuclear cells, mixed with a few polynuclear leucocytes. The mononuclear cells, as a rule, approach the plasma cell type. Compressed plasma cells sometimes occur singly or in pairs in the walls of small vessels in the nerve-cell layers of the cortex. For the most part there is very little sign of exudate in the deeper layers. The cells about the smaller vessels near the abscess are swollen and increased in number. Cells in apposition with the vessel walls are occasionally seen in mitosis. The nerve cells have undergone a variety of changes which are chiefly the product of edema—swelling and vacuolation, shrinkage and chromophilia, extrusion of nucleolus. The satellite cells occur often in groups of eight or ten, about the small pyramidal nerve cells, which are themselves, as a rule, in some degree altered. The satellite cells fail to show well-defined cell bodies or any sign of inclusions. There seems to be evidence that nerve cells may occasionally disappear from the midst of satellite cell groups. No mitoses were observed among the satellite cells in this case. Near the abscess there are a few nuclear figures in large cells, some of which had numerous vacuoles in their cell bodies outside the spindles. It is doubtful whether these figures occur in endothelial or neuroglia cells. There is little evidence of cell cavity. In the areas of frank hemorrhage here and there is a phagocytic cell containing blood globules.

The lining of the ventricle is macerated. There is rarely any evidence of proliferation in the lining cells. In places the wall is supplanted by masses of fibrin containing exudative cells. The vessels of the underlying tissue are dilated, sometimes to an unusual degree, and the sheaths of the veins are filled with cells of the lymphocyte series, including many examples of the plasma cell. Mitotic figures are scattered at rare intervals through the edematous tissue underlying stripped portions of the ventricular lining. One skein form was found in a highly vacuolated cell which lay free in a collection of blood globules. Otherwise the tissue shows merely degeneration or necrosis. In some cases the small cells near the nerve cells share their chromophilia, but in other cases the small cells appear to stain densely at a stage when the nerve cells are still fairly well preserved. The tissue under the ventricle appears to have been more directly subject to injury than the tissues about the subcortical abscess, so that there is here more sign of degeneration than of the cell proliferation seen about the abscess.

CASE 3.—R. R., male, aged 53, was admitted to the service of Dr. A. L. Mason at the Boston City Hospital, April 21, 1901.

Clinical History.—Patient had been in bed three weeks before admission; malaise, weakness, headache, dizziness. On admission cheeks were flushed, slight left internal strabismus, pupils small; otherwise all signs were negative. The day after admission temperature rose to 102, patient became restless and noisy and tremor of extremities set in. April 24, ascites, dribbling of urine, mild delirium, Cheyne-Stokes respiration. April 26, incontinence of feces, rigidity of neck. April 29, patient unconscious and quiet, respiration rapid and superficial. Death.

Autopsy.—The autopsy, performed by Dr. E. E. Southard twenty hours after death, showed:

Head: Calvarium and dura normal. Longitudinal sinus filled with dark fluid blood. Subdural space shows marked increase of fluid; probably 300 c.c. leaks away. Pial vessels injected, pia over sulci opaque and tense from contained fluid. There is considerable web-like, thinly-spread opaque connective tissue in basilar region, especially around optic chiasm and in Sylvian fossæ. Brain substance is very soft; corpus callosum like Neufchatel cheese. All tissues are moist. Puncta cruenta distinct on section of centrum semiovale. There is about a test-tubeful of clear fluid in each lateral ventricle.

Cord: Much clear fluid under tense dura. Cord tissue is firm and well shaped, but over all is a thin, glistening, opaque-white deposit, slightly more marked in lumbar region. Foramen of Magendie and accessory foramina are occluded by this overgrowth. Middle ears normal.

Anatomic Diagnoses.—Basilar and spinal organizing meningitis. Internal hydrocephalus. Increase of subdural fluid. Edema of brain. Fatty degeneration of heart muscle. Slight fatty degeneration of renal epithelium. Congestion of spleen, liver, kidney, pancreas, bladder mucosa. Chronic pharyngitis. Hypostatic pneumonia. Chronic adhesive pleuritis. Chronic perisplenitis. Chronic interstitial orchitis.

Microscopic Findings.—Cultures from heart's blood and lung showed *Streptococcus pyogenes* and many other organisms. The liver showed *B. coli.* The tissues at the base show considerable variety in exudate. The looser tissues contain fibrin and polynuclear leucocytes, which outnumber the other kinds of cell. The adventitiæ of the vessels contain numerous cells of the lymphocyte series.

Intimal lesions, although prominent in arteries of smaller caliber, spare the larger arteries. The intimæ of the smaller arteries are lifted or completely dissected off by an exudate composed chiefly of cells of the lymphocyte series, among which are examples of the typical plasma cell. Between the loosened intima and the elastic layer of the artery there may be deposited a dense, deeply-stained sheet of fibrin. In late stages of the lesion, when the intima has scaled off, the appearances simulate a fibrinous transformation of the intima. The smaller vessels are often wholly blocked by masses of fibrin and desquamated cells. The nerve tissue beneath the exudate is edematous and shows nerve cells in various stages of injury, retaining, as a rule, well-staining nuclei. Single leucocytes invade the pons tissue for several millimeters. There are a few narrow marginal areas of nerve tissue replaced by fibrin and leucocytes. The cord shows an exudate of cells of the lymphocyte series and well-developed vascular lesions resembling those at the base of the brain.

Case 4.—H. W., male, aged 31, was admitted to the service of Dr. Henry Jackson at the Boston City Hospital, July 30, 1903.

Clinical History.—There had been persistent emesis without gastric pain or distress, three weeks. Dizziness, frontal headache, blurring of vision, swelling of feet and ankles, slight cough with expectoration. Stopped work two days before admission. Urine contained albumin and casts. Diagnosis, chronic interstitial nephritis. Discharged four days after admission. Readmitted Sept. 10, 1903. Heart enlarged; soft systolic murmur at apex transmitted to axilla. Heart and kidney signs grew gradually worse. Mind not clear. Oct. 14, 1903, erysipelas set in; developed rapidly to sloughing of eyelids with severe chills. Death Oct. 15, 1903.

Autopsy Findings.—The autopsy, performed five hours after death by Drs. R. E. Lee and E. E. Southard, showed:

Head (Dr. E. E. Southard): Scalp is everywhere edematous, ranging from 2 to 3 cm. in thickness. Tissues over frontal eminence and orbits are brawny and hard to turn back. Calvarium of normal thickness, without diploë. Dura of normal tenseness and thickness. Moderate injection of middle meningeal system. Sinuses filled with fluid blood and cruor clot. Meshes of pia distended with cloudy (fibrinous) fluid, without cellular exudate. Arachnoidal villi moderately well developed. Substance moist. Ventricles showed no increase of fluid. Interbrain, midbrain and bulb normal. Vessels at base normal.

Middle Ears: Right normal. Left contains greenish fluid pus with streptococci. Ethmoid cells normal. Orbital tissues are infiltrated with greenish pus containing streptococci. Eyes removed from behind show fairly clear conjunctivæ, with impression of opacity behind, especially marked in left eye.

Anatomic Diagnoses. — Chronic diffuse nephritis. Hypertrophy of heart. Slight fatty myocarditis. Erysipelas of face. Acute purulent conjunctivitis. Edema of pia and of substance of brain. Acute otitis media (*streptococcus*).

Purulent infiltration of orbits (*streptococcus*). Slight bronchopneumonia. Chronic obliterative pleuritis (left). Fatty liver. Edema of glottis. Hydrothorax.

Microscopic Findings.—The exudate into the pial tissues consists of slight edema with exudative cells almost invariably mononuclear, mainly lymphocytes. There is an occasional polynuclear leucocyte. The only signs which can be connected probably with the septicemia are in some of the small arteries. These show desquamation of endothelium, with dense fibrin deposits on the elastica. The elastica in these arteries, which are in certain cases entirely plugged by leucocytic thrombi, fail to contract in the usual wave form, but remain smooth and flat. There is no considerable neuroglia reaction in the subpial layer or elsewhere.

Case 5.—J. B., male, aged 19, was admitted to Dr. G. A. Leland's service at the Boston City Hospital, Dec. 30, 1903.

Clinical History. — Patient had had measles as a child. There had been discharge from right ear for six years, with occasional attacks of pain and fever. External abscess once opened by family physician. Two weeks before admission a similar attack was followed by severe, continuous, generalized headache. Temperature 102 two days before entrance. Pain localized in occipital region, radiating to interscapular region. Neck rigid. Leucocytes, 24,000. Right mastoid operation (Dr. Leland). Temperature dropped to 100. Leucocytes, 16,000. Slight rotary nystagmus, more marked in right eye. January 1: Right facial paralysis. January 3: Pupils dilated, right more than left; fundus examination showed haze of both discs with congestion of lamina cribrosa and venous engorgement. Vomiting. Restlessness. Second operation by Dr. Leland; exploration of cerebellum. Apparent improvement. Vomited once. Pain in occiput allayed by morphia. Wound dressed under primary ether, January 5. Afterward delirious, crying with pain in head. Morphia. Delirium once more, followed by coma, morning of January 6; respirations 6 to 8; pulse not countable and intermittent. Death.

Autopsy Findings.—Examination, limited to the head, made by Dr. E. E. Southard 2¼ hours after death; showed scalp veins filled with fluid blood. Tissues adjacent to lips of wound gray and chocolate-brown, edematous and friable. The necrosis involves the mastoid insertions of the right sternomastoid, splenius capitis, and trachelomastoid muscles: head drawn forcibly to the left. Rigor absent. Tissues warm.

Calvarium thin, rarely reaching .5 cm. Right temporal bone removed intact by sawing shows thumb-sized cavity of the mastoid exenteration and perforations made for exploration of posterior fossa cerebri (cerebellum and temporosphenoidal lobe).

Dura of the usual thickness, lightly adherent opposite bregma, can not be picked up readily with forceps. Small perforations are found in outer portion of right posterior fossa cerebri. Localized on dura covering posterior surface of petrous portion of temporal bone, involving meatus internus and aqueductus vestibuli, is a layer, .2 to .4 cm. deep, of granulation tissue with thick fibrinous greenish-gray pus. Sinuses contain fluid blood. Tissues about right superior petrosal sinus soaked in pus.

Pia shows moderate injection, chiefly of the large veins of sulci, over vertex and sides. Meshes of pia under interbrain floor are filled with tenacious greenish pus which follows both Sylvian arteries for a few centimeters into fossæ Sylvii and follows anterior choroid arteries for some distance. Optic nerves are held in edematous purulent fibrous tissue; nerves look redder than usual on section. Slender processes of fibrin containing pus enclose anterior communicating and anterior cerebral arteries; leaves of pia in this region are somewhat firmly united. Pituitary not grossly involved. Pia over pons is distended with plastic layer of greenish pus. Considerable clear fluid is found between pia and dura. Pia over cerebellum contains no pus except immediately over abscesses, but the subdural space of the right posterior fossa contains considerable purulent fluid.

Ventricles: The posterior horns of both lateral ventricles, the anterior horn of right lateral ventricle and floor of third ventricle contain slight plastic deposits of greenish pus and fibrin, apparently settled out of a considerable surplus of turbid brownish fluid distending the cavities. The ependyma of the ventricles is swollen, deeply velvety and peels away in a clinging layer .1 to .2 cm. thick. Fourth ventricle is lined with what resembles an early pyogenic membrane, which can be peeled away readily, leaving an edematous ependyma with deep red punctation.

Substance: Sulci of hemispheres are almost effaced. Substance is moist. Very little injection either of cortical or of central ganglionic vascular systems. The substance of the right cerebellar hemisphere external to flocculus contains a greenish abscess cavity 2 x 2 cm. across, of an indefinite depth. The edema and a slightly greenish color invade the dentate nucleus playing out vaguely. Injected tracks of director (used for exploration) are found in cerebellum and temporosphenoidal lobe. The abscess is just missed by the exploration. Interbrain, midbrain, and isthmus are normal on section. Weight (minus considerable fluid) 1490 gm.

Anatomic Diagnoses.—Mastoid operation. Exploration of cerebellum and temporosphenoidal lobe. Chronic otitis media. Abscess of cerebellum. Acute fibrinopurulent basal leptomeningitis. Pyocephalus internus. Edema of substance with flattening of gyri.

Microscopic Findings.—Culture from brain showed streptococci.

The cortical meninges at the vertex show a thin layer of large mononuclear cells of the phagocytic type. One of these occasionally contains a polynuclear leucocyte.

At the base the exudate is often 3 to 4 mm. thick and varies according to its relation with vessels. The free exudate shows numerous cells of the phagocytic series, together with polynuclear leucocytes and cells of the lymphocyte series in about equal numbers. The adventitiæ of the veins contain chiefly cells of the lymphocyte series. The tissue at the base is the only region examined in this case which shows marked lymphocyte infiltration.

The cerebellum shows an exudate which is deepest in the sulci between the outermost laminæ and beneath the superficial pia mater. There is focal invasion of the molecular layer by leucocytes, either singly or in very small groups; but, beyond there, there is no evidence of either gross or selective injury to the nerve tissue. The exudate shows polynuclear leucocytes very prominently; but counting shows that they rarely exceeded the mononuclear exudative cells in number. Of these mononuclear cells the most prominent are large cells with eccentric vesicular nuclei, which are phagocytic for polynuclear leucocytes. About a few small veins are collections of cells of the lymphocyte series; for these cells the larger mononuclear cells fail to be phagocytic, save in rare instances.

The choroid plexus shows numerous cystic spaces about the larger vessels. The spaces contain granular material and numerous corpora amylacea. The acute inflammatory reaction fails to involve the central regions of the plexus, but is strikingly shown immediately below the ependyma in many folds. The deepest exudate occurs at the tips of certain folds, where the polynuclear leucocytes sometimes accumulate in masses and dissect off the epithelium. Numerous folds are wholly spared from exudate. It is not possible to give a reason for the variations shown. As a rule the epithelium is well preserved and shows many of its characteristic vacuoles. An occasional leucocyte is caught in emigration between the epithelial cells. Cells of the lymphocyte series are almost never in evidence. Between the folds there is considerable granular material with polynuclear and desquamated ependymal cells.

The floor of the fourth ventricle fails to show the pyogenic membrane suggested in the gross. The gross appearance was produced by an extensive local acute infiltration and formation of fibrin which permitted stripping off the superficial gray matter in a single mass. The fibrin collects particularly in the walls of small vessels, many of which are no longer pervious. The most prominent cells in the subependymal tissue are polynuclear leucocytes, some of which approach closely or seem to bury themselves in dying nerve cells. The neuroglia reaction does not go beyond swelling and process formation in the cell bodies.

At the edge of the abscess the intima of the arteries is raised by polynuclear leucocytes and may be stripped away. The large vessels remain pervious; it is probable that the smaller vessels become blocked at their origins. The abscess contains considerable fibrin. The polynuclear leucocytes far outnumber the mononuclear cells which are chiefly of the type with vesicular nuclei. The mononuclear cells in the free exudate are not very often phagocytic. The optic nerve shows edema and exudate of polynuclear leucocytes, together with a few phagocytic cells, in both the subarachnoid and subdural spaces.

Case 6.—C. W., a male, aged 52, was admitted to the service of Dr. J. L. Ames at the Boston City Hospital, Jan. 21, 1904.

Clinical History.—Gonorrhea at twenty-seven. Rheumatism for ten years. Heavy drinker. Little alcohol for four days. The day before entrance fell while riding on car platform, procured one drink of whisky, lost consciousness and was brought to hospital. On admission dull, tremulous. Showed systolic murmur at apex transmitted to axilla and systolic whiff in arteries. Arteriosclerosis. Reflexes normal. Delirium with motor excitement set in but was replaced later with prostration. Slight nystagmus and deviation of eyes to right; pupils equal, reacting to light. Pulse rose to 160, respiration to 60, temperature to 105. Some spasticity of arms and legs. Râles appeared over both chests. Death, Sept. 26, 1904.

Autopsy Findings.—The autopsy, performed four hours after death by Drs. R. L. Thompson and N. H. Gifford showed:

Head: Hair black and fairly thick. Scalp normal. Calvarium thin. Dura adherent to calvarium. Sinuses contain cruor clot. Arachnoidal villi are fairly well marked. Meshes of pia contain over 50 c.c. cloudy, greenish-yellow, fairly thin fluid. Greenish and yellowish-white, fine and coarse thread-like markings along pial sulci. Both small and large vessels are moderately congested. Vessels of circle of Willis show slight diffuse thickening. Convolutions are well rounded and of fairly soft consistence with slightly congested vessels. Ventricles contain a few c.c. clear and pale yellow fluid. Cysts (1 to 3 mm. in diameter) stud choroid plexuses of both lateral ventricles. Pons and medulla of reduced consistence. Substance on section shows nothing remarkable.

Spinal cord: Fluid turbid. Pia thick and greenish-yellow. Cord soft.

Anatomic Diagnoses.—Acute leptomeningitis and encephalitis. Acute bronchitis. Edema and congestion of lungs. Chronic mitral endocarditis. General arteriosclerosis. Chronic splenitis. Chronic fibrous pleuritis. Chronic fibrous pericarditis. Chronic external pachymeningitis. Apical scar of left lung. Cysts of choroid plexus.

Microscopic Findings.—Cultures from heart's blood, lung and brain showed pure *Streptococcus pyogenes;* from liver, spleen and kidney, *Streptococcus pyogenes* and *B. coli.*

The cortical meninges are edematous and contain an exudate of polynuclear leucocytes which enclose numerous pairs of streptococci. Numerous chains of streptococci lie free in the granular material deposited in the pial meshes. Large phagocytic cells are rare. Single polynuclear leucocytes are found at rare intervals imbedded in the intima of the arteries; mononuclear cells are still rarer in this locus.

The severest lesion in this case affects the large sulcal veins, whose walls may be distended with polynuclear leucocytes outnumbering the original cells making up the wall. In the neighborhood of the injured veins there is an accumulation of large mononuclear cells; but these fail to be phagocytic in many cases, either for polynuclear leucocytes or for bacteria. Next to the severely injured veins, the larger arteries also exhibit the deepest infiltration of the intima with polynuclear leucocytes. The spinal meninges show an early exudate with few large phagocytes. Vascular lesions were not prominent in the blocks examined.

Case 7.—L. H., a girl baby, born Dec. 25, 1904.

Clinical History.—Breast fed, had a cold at five weeks, but rapidly got well of it. The mother had sore throat, pain in back and legs, and fever when her child was about seven weeks old; the child at this time showed nothing but slight distension of the abdomen. A temperature of 104 appeared Feb. 23, 1905, throat and chest were negative. Admitted to Massachusetts Infants' Asylum with pulse 136, temperature 103, weight 5,000 gm. There was a slight red area on the left leg, attributed by the mother to a burn. The next day this red area had spread; the knee swelled; the head was held retracted. February 25, the whole left leg was swollen and tender but without increase of temperature, respiration shallow and grunting. The body temperature was maintained above 101. The leg improved; the morning of February 28, jaundice and convulsions appeared; general twitching, legs flexed, arms flexed across chest. The throat became filled with mucus. The chest showed râles, probably transmitted. March 1 the jaundice had increased, the head was held retracted, there was an occasional general twitching. The child vomited and failed to take food well. The eyes were fixed, the pupils dilated and sluggish. Death at midnight.

Autopsy Findings.—Examination 12 hours after death by Dr. E. E. Tyzzer showed: Murky limpid fluid beneath dura. Pial meshes contain murky bile-stained exudate. Exudate thick over cerebellum, thinner over cord. Murky bile-stained fluid exudate in ventricles.

Anatomic Diagnoses.—Acute cerebrospinal meningitis (*Stereptococcus*). Septicemia. Icterus (gall bladder and ducts normal).

Microscopic Findings.—Cultures showed *Streptococcus pyogenes* pure in heart's blood and liver, mixed with a *Staphylococcus* in spleen.

Cortex Cerebri: The meshes of the pia mater are distended with cells, of which the large mononuclear cells greatly outnumber the rest. The large mononuclear cells are phagocytic for numerous pairs and chains of streptococci. The inclusion of other exudative cells is frequent, but by no means so prominent as the bacterial phagocytosis. Large phagocytes of an omnivorous character are found, with vacuoles containing fat, mononuclear cells, polynuclear leucocytes and bacteria. Polynuclear leucocytes are frequent, but tend to show signs of degeneration. Cells which can be identified as belonging to the lymphocyte series are not frequent. A few cells of the plasma cell type, occasionally with two nuclei, lie in the adventitiæ of the vessels.

Cerebellum: The exudate varies in character, but shows everywhere a certain number of polynuclear leucocytes. Colonies and chains of streptococci abound in the superficial pia mater, and as a rule are enclosed within cells, both within polynuclear leucocytes and within large phagocytic cells. The bacteria seem to pass through an eosin staining stage before complete digestion. Except in the deepest places of the exudate opposite the mouths of the sulci, the polynuclear leucocytes are outnumbered by the large phagocytic cells. It is not infrequent to find cells phagocytic for polynuclear leucocytes which are themselves phagocytic for bacteria. In the sulci the connective tissues are packed with large vacuolated cells which accommodate themselves readily to changes of shape in the spaces they occupy. There are a few cells of the lymphocytic series, often with vesicular nuclei or with chromatin not murally arranged; but cells of the finished plasma cell type are rare.

Spinal Cord: The large phagocytes containing several kinds of cells and bacteria are prominent in the looser tissues. The adventitiæ of the vessels contain also a moderate number of cells of the lymphocyte series. The arteries show intima occasionally lifted by edema, with rarely an exudative cell beneath.

Case 8.—C. H., a hydrocephalic imbecile, aged 45, entered Dr. H. W. Mitchell's service at the Danvers Insane Hospital Oct. 13, 1905, and died Jan. 24, 1906.

Clinical History.—Dull at school. "Always ailing." Never could earn his living. Became vagrant several weeks before admission. Impairment of memory. Romberg sign absent. Gait fairly steady. Coarse tremor of fingers. Left pupil slightly irregular and without reaction. Knee jerks lively. Achilles reflexes brisk, with slight clonus. Plantars present. Spurious clonus of both ankles. Arm reflexes lively. Movements slow and listless. No spontaneous conversation. Memory poor. Limitation in range of thought. Lack of ideation.

Fainting spell two weeks before death. Decubitus. Pneumonic area in right lung. Death.

Autopsy.—Autopsy, performed by Dr. E. E. Southard, showed:

Head: Hair is gray and thin. Scalp strips readily. Calvarium thin, without diploë. Dura not adherent to calvarium. Dura distended. Sinuses contain liquid blood. Arachnoidal villi in moderate amount. Dura strips readily from pia except over ascending frontal gyri, where, particularly on the left side, the dura and pia are gummed together by a plastic stringy yellowish-gray exudate, covering an area on each side scarcely larger than a dollar and thinning out gradually at edges. There is no gross connection between this exudate and the otitis media of the right side. Except at the vertex, the pia mater is without exudate or edema and shows a few fibrous streaks over sulcal veins. The substance of the brain, cerebellum, interbrain, pons and bulb, exclusive of fluid contained in the ventricles, weighs 960 gm. The fluid withdrawn from the ventricles measures 1,300 c.c. The sulcation of the brain is rich but chiefly superficial and gives the impression of an alligator skin bag. The pia strips readily from the substance. Many of the sulci run inward for a few millimeters and bend at right angles, assuming a position concentric with the hemisphere surface for a few millimeters. It is not possible to homologize the sulci found with the sulci of the normal brain. The Sylvian fossa is the sole landmark on the flank of the hemisphere. Incision of the ventricles and withdrawal of the contained clear liquid show basal structures of a normal appearance, but almost total absence of callosal and fornix tissue. The walls of the ventricles are thinnest above and thickest below and behind. At the vertex the cortex and underlying white matter measure in places no more than 1.5 cm. The walls of the ventricles are of smooth and normal appearance. The cerebellum is of normal appearance and consistence. Lower structures are grossly normal. Right middle ear contains semi-liquid yellowish-green pus communicating with a cavity 1.5 cm. in diameter, in the mastoid process.

Anatomic Diagnoses.—Purulent otitis media dextra. Localized purulent leptomeningitis (vertex). Congenital internal hydrocephalus, with atrophy of corpus callosum and fornix and with microgyria and thinning of cortical substance. Absence of diploë. Slight aortic sclerosis. Apical scar of left lung. Edema and congestion of posterior parts of lungs. Cholelithiasis.

Microscopic Findings.—Culture from left middle ear shows *Streptococcus pyogenes.*

Cortex Cerebri: Phosphotungstic hematein section shows diffuse loose meshed neuroglia tissue with delicate isolated fibrils running in all directions. In the cell layers of the cortex the fibrils are curly, but run, as a rule, radially. Just below the pia, they begin to run tangentially and unite in a thin, dense mat. The deposit is thickest at the bottom of the sulcus, and there are sometimes projections of glia into the pial tissues in this situation, recalling the picture of *Randsklerose*. Some of the cells of the subpial region show two or three centrosome-like bodies in a light space in the cell body. The gliosis is remarkably even and delicate and is not markedly perivascular.

Cortex with Exudate (Frontal Region): Hemorrhage, with numerous polynuclear leucocytes and mononuclear cells in about equal proportions. Many of the mononuclear cells are phagocytic for polynuclear leucocytes.

The neuroglia cells beneath the pia have swollen bodies; some have two or three nuclei.

Cortex from Various Regions of Right Hemisphere (Nissl Stain): Superior frontal, ascending frontal, ascending parietal, paracentral, calcarine, limbic, gyrus rectus, show unusual cell pictures characterized by an unusual relative cell richness suggesting the pictures presented by the cortex of lower animals. The richest cell picture is derived from the calcarine area. Right Ammon's Horn (eosin methylene blue, phosphotungstic acid hematein) shows a thin superficial fibrillary gliosis with delicate even fibrils, and centrally a regular rich felt work of even delicate fibrils with some stouter ones.

Choroid Plexus: Numerous concentrically-layered bodies, Villi few. Vacuoles few.

Caudate Nucleus: Nerve cells as wide apart as usual. The ventricle wall shows flattened cells having basal corpuscles (phosphotungstic acid hematein) but, as a rule, no cilia. There are no elevations like those in more acute internal hydrocephalus.

Cerebellum: Centrum album gyrorum apt to be slender.

Cord: Nissl sections show an occasional eccentric nucleus in anterior horn cells at several levels. Phosphotungstic acid hematein demonstrates no excess of neuroglia.

The striking point exhibited by this case is the reaction of the neuroglia to the acute leptomeningitis. This reaction is a cellular gliosis resembling in every detail the cellular gliosis of the normal adult brain. Although the case showed very slight resistance to the streptococcus infection of the middle ear, yet the cells of the meninges showed phagocytic tendencies resembling those of the normal adult meninges, and, so far as demonstrable, the polynuclear leucocytic exudate was in the process of clearing up by the mononuclear cells.

Case 9.—J. O., a woman, aged 40, entered Dr. F. R. Sims' service at the Danvers Insane Hospital April 4, and died April 9, 1906.

Clinical History.—Headache, violence, delusions of persecution, incoherence, four days before entrance. Nursing child thirteen months old. Herpes of lips, skin lesions probably due to chafing, constant listlessness. Lay on right side with head retracted and drawn to left and eyes turned up and to the left. Gait tottering, with feet held wide apart. General tremor. Knee-jerks apparent. Babinski reflex doubtful. Limbs held rigid. Pupils widely dilated. Resistive, distractable, disoriented. Fever 103. Signs of pneumonia in right lung set in three days after admission. Death.

Autopsy.—Autopsy, performed by Dr. E. E. Southard, showed:

Head: Hair dark. Scalp normal. Calvarium thick, with abundant diploë. Two emissary vein foramina in parietal bones. Dura lightly adherent to calvarium in bregmatic region. Dura tense, not markedly injected. Sinuses contain liquid or freshly clotted blood. Superficial cerebral veins deeply injected. Dura and pia inter-adherent in region of arachnoidal villi, through yellowish, very fibrinous pus. Fine superficial injection of vessels everywhere, but very little congestion of veins except at vertex. Pia externally smooth and only slightly moister than usual. The sulci and gyral surfaces are in a few regions filled with yellowish fibrinous pus: the upper two-thirds of both fissures of Rolando, the upper thirds of both ascending parietal gyri and, to a less extent, the upper thirds of both ascending frontal gyri, both superior parietal lobules, both fossæ of Sylvius. The circle of Willis is wholly concealed by fibrinous pus. The cisternæ of the base are filled with cloudy liquid. The middle two-thirds of the basilar artery is covered with fibrinous pus. The loci of origin of the fifth nerves are marked by masses of pus. The pia over culmen monticuli is swollen to a depth of .5 cm. with pus. The great horizontal fissure of cerebellum contains stringy yellowish pus.

Brain weight, 1,310 gm. Gyri a trifle flatter than normal. Substance everywhere equally reduced in consistence. The olives are no harder on palpation than the remainder of the medulla. Cerebellum softer relatively than cerebrum, softest in vermis which in places is almost diffluent. The line of Gennari in the cerebrum is hard to make out. There is no focal difference in consistence in the cerebrum, even in the areas of most marked suppuration.

Ventricles contain a normal or only triflingly increased amount of fluid which is cloudy. At the tip of each posterior cornu is a small mass of fibrinous pus. There is no pus in third or fourth ventricles.

Cord: On incision of the lumbar dura, considerable cloudy liquid flows out under slightly increased tension. Dura everywhere pinker than usual. Pia everywhere cloudy, but puffed out with yellowish fibrinous pus in cervical, middle thoracic, and lumbar regions notably behind. The root ganglia are frequently swollen.

Middle ears both free from pus. Cribriform plate apparently normal. Sphenoidal sinus filled with fibrinous pus. Nasal mucosa of right side swollen, injected, on left side apparently normal. Pituitary body soft, shows traces of pus on upper surface. Optic nerves, third nerves Gasserian ganglia (notably beneath), to a less extent seventh and eighth nerves, are surrounded by pus as they leave cerebral dura. Left retina excised; shows no injection.

Anatomic Diagnoses.—Acute cerebrospinal leptomeningitis. Serofibrinous exudate of vertex, Sylvian fossa, interpeduncular space, pons, vermis and horizontal fissure of cerebellum, pia of cord, origins of cranial and spinal nerves, Gasserian and spinal root ganglia. Acute purulent internal hydrocephalus and seropurulent exudate in cisternæ. General edema of brain and cord, particularly of vermis of cerebellum. Empyema of sphenoidal sinus. Edema of lungs. Bronchopneumonia of both lower lobes. Herpes labialis. Numerous minute hemorrhagic lesions of back and thighs. Acute splenitis. Acute and chronic nephritis. Slight aortic and mitral sclerosis. Extra cusp to pulmonary valve. Chronic adhesive pleuritis (bilateral).

Microscopic Findings.—Smear from sphenoidal sinus shows tremendous numbers of organisms, probably all streptococci. Smear from vertex shows great numbers of polynuclear leucocytes and mononuclear cells but no organisms. Smear from purulent fluid of basal cisternæ shows a very few pairs of small diplococci within leucocytes. The results of blood serum cultures confirmed the findings by smear.

Examination of the tissue in this case, showed a remarkable variety of pictures. Leptomeningitis, although fatal, was in the process of clearing up. This clearing-up was taking place from above downward. The pus at the vertex, about the longitudinal sinus and in pial meshes was sterile. The dominant cells were mononuclear. They contained numerous polynuclear leucocytes and fragments of nuclear material, besides considerable fat. No organisms could be found in these tissues. The picture thus resembled that in a healing leptomeningitis of meningococcal origin.

The pus at the base, on the contrary, contained a few pairs or short chains of an organism, which proved to be *Streptococcus pyogenes* in culture. The meshes of the pia at the base showed a higher proportion of polynuclear leucocytes than the pus at the vertex. Mononuclear phagocytosis was in process; but the healing must be regarded as in a far earlier phase than that of the vertex.

Traversing the bone at the base of the brain and examining the mucosæ of the sinus, a picture of acute inflammation is found. The polynuclear leucocytes here far outnumber the mononuclear cells and the tissues are filled with countless chains of streptococci. The general picture in this case anatomically resembles that in a meningococcus case of meningitis. The clearing up of the exudate takes place irregularly and from above downward.

GENERAL CLINICAL SUMMARY.

Seven patients were male, two female. Seven patients were over 30 years old; two of these over 50. One was nineteen, one an infant. Five cases showed otitis media.

DURATION OF ACUTE SYMPTOMS.	DURATION OF CEREBRAL SYMPTOMS.
Case 1—4 weeks	24 days
Case 2—24 days	3 days
Case 3—4 weeks	4 weeks (8 days?)
Case 4—13 weeks	Brief
Case 5—Chronic middle ear (6 years), 24 days	24 days
Case 6—7 days	7 days
Case 7—7 days	7 days
Case 8—2 weeks	2 weeks
Case 9—10 days	10 days

As will be seen by comparison with the durations in a series of pneumococcus cases reported by Southard and Keene,[2] the durations in these streptococcus cases run a trifle greater than in the pneumococcus cases.

GENERAL ANATOMIC SUMMARY.

The brain lesions vary in character and distribution. The leptomeninges showed lesions in all cases. Cases 4 and 3 were exceptional. Case 4 showed distension of the pial meshes with a flocculent liquid exudate (which might readily simulate the so-called meningitis serosa). On the other hand, Case 3 showed an opaque tense pia mater of the vertex, with a thin web of organizing tissue at the base (simulating the appearance of a late meningococcal infection). The other seven cases all showed a more cellular exudate, variously described as thick, tenacious or fibrinous, and as opaque yellowish or greenish in color.

The distribution of the pial exudate is interesting. Except the hydrocephalic (Case 8), the base showed exudate in all cases, if we include the serous case (Case 4); if we include Case 4 as an exudative case, in all cases except Case 3 (organizing) and Case 5 (fulminant operative case). The cord is involved from the base, as a rule, the ventricles from the base or from abscesses of the substance adjacent to the ventricles.

The lesions of the brain substance are various. Flattening of the gyri stands in close relation with involvement and probably with actual distension of the ventricles. When flattening is absent, the substance is soft and moist and may be finely injected. No case of cortical flattening fails to show exudate in the ventricles; but in early stages of ventricular exudation the sulci may flare normally. Frank abscesses occurred in Case 2 (right temporal lobe) and Case 5 (right cerebellar hemisphere).

Cases 1, 2, 4, 5, 8 showed otitis media. Of these Cases 1, 2, 5 came to mastoid operation. Case 4 was an erysipelas case. The nasal sinuses were affected in Case 9. Of the others Cases 3, 6, 8, 9 showed lung lesions, which can not be certainly brought into relation with the leptomeningitis. Case 7 showed septicemia with icterus. Decubitus of one buttock occurred in Case 1, in multiple areas in Case 8, hemorrhagic cystitis in Case 2.

Of chronic lesions, whose relation to the infection can not be asserted, the following occurred: arteriosclerosis in Cases 1, 4, 9; chronic pleuritis in Cases 1, 2, 3, 4, 6; chronic internal hydrocephalus in Case 8.

GENERAL SUMMARY OF MICROSCOPIC FINDINGS.

As in previous work with cases of *Staphylococcus pyogenes aureus* and of pneumococcus brain infections, alterations were found in several of the tissues. The lesions of the streptococcus series present a close resemblance to those of the pneumococcus series. Characteristic for both organisms are the lesions of the vessels. The vascular lesions (described in more detail in the paper on pneumococcus infections) may serve to distinguish the pneumococcus-streptococcus cases, as Dr. Councilman has suggested, from meningococcus cases, It would be less easy to distinguish these vascular lesions from those in tuberculous leptomeningitis, in which the occurrence of local necrotic areas might need to be considered in making a diagnosis from the tissues. With a sufficiently long series of cases, it might be possible to mark out, from the vascular lesions alone, the course of the disease leptomeningitis.

Not merely the vessel lesions, but also the meningeal exudates serve in their variety to show how complex is the question of the natural history of leptomeningitis. As indicated in the two former papers,[1, 2] the occurrence of exudates with numerous mononuclear cells of the lymphocyte series is in itself not sufficient to differentiate any one type of leptomeningitis, such as the tuberculous, the syphilitic, the general paretic. Plasma cells are ubiquitous. The meninges exhibit exudates of a very variable character in many infections and toxic conditions. Perhaps it is not immediately necessary to ascribe the variations of exudate to different qualities of pathogenic agent. It will be desirable to work out first the time relations of a few organisms.

GENERAL SUMMARY AND REMARKS.

The foregoing cases of streptococcus brain infection are of interest in comparison with the cases of pneumococcus brain infection described last year. The main results may be stated in connection with those of the pneumococcus study.

As with the pneumococcus series, the questions of main interest are brought up by the varying extent and effect of lesions like (1) arteritis and phlebitis, (2) the cellular infiltration of the meninges with its variation in respect to phagocytosis and (3) the attendant cellular and, in certain cases, fibrillar gliosis.

Clinically viewed, the cases are of various duration and run a trifle longer than the pneumococcus cases. The relation of streptococcus meningitis to lung lesions is less suspicious than that of staphylococcus or pneumococcus brain infections to lung lesions. The part played by lung lesions in bringing about meningitis has probably been overestimated. The streptococcus cases seem to be more pronouncedly "cerebral" or "meningitic" from the very start of acute symptoms than are the pneumococcus and staphylococcus cases, which are a little more "primary."

Anatomically viewed, the streptococcus cases preserve their resemblance to the pneumococcus cases. even to the production in some cases of small abscesses. Particular attention may be called to the case simulating meningitis serosa (Case 4). It would be well to review the cases of this disease to be found in the literature and exclude those without bacteriologic examination.

Considered histologically, the streptococcus cases again resemble the pneumococcus cases. The same relations of bacteria to leucocytes, of leucocytes to cells of the macrophage type are shown in the two series. The intimal infiltration of the arteries and the intimal proliferation and exudative lesions of the veins run parallel in the two cases. The occurrence of early fibrillar gliosis (in the sense of the production of new fibrils by the swollen neuroglia cells) is important. The interpretation of early fibrillar gliosis is not easy, since it is necessary to exclude extraneous causes (old age, arteriosclerosis, chronic active lesions) for its occurrence.

An extensive series of guinea-pig inoculations, which need not be reported in detail, confirmed the main result, viz.: the parallelism in action of the two organisms, pneumococcus and streptococcus. Orbital inoculations simultaneously in numerous animals with histologic examination of animals killed on successive days were employed as in previous work. The inoculations of the strains used, as a rule, produced no clinical sign, despite the suppuration present. As in the human cases, each of the lesions found is apparently wholly curable taken by itself.

The reversible character (to use a phrase from books of logic) of the phenomena is shown in the strikingly various pictures presented by the exudate in Case 9 taken from the vertex downward.

Indeed, it is rare to find in streptococcal, as in other forms of acute leptomeningitis, any single lesion which is necessarily incurable. It is probable that in many cases the patients die of toxemia. This toxemia may vary with the extent of the exudate. The amount of exudate which we see at an autopsy may mislead us in our idea of the proportions of the toxemia, since wide reaches of the pia mater may be sterile, though other parts contain multiplying organisms. Differential studies of the exudate in several places are essential if we are to get a fair sample of the conditions. Such studies might readily assume clinical importance.

The early glioses found in several cases are of some importance both in general and clinically. These glioses will be best considered in connection with those in tuberculous meningitis in a subsequent paper.

X

LESIONS OF THE GRANULE LAYER OF THE HUMAN CEREBELLUM.*

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The granule layer of the cerebellum is peculiar in construction. The layer is very rich in cells, surpassing most regions of the nervous system in the proportion of cells to the unit of space. Very noteworthy, in comparison with the general cell wealth, is the relative paucity in this locus of interstitial substance. Barring its vessels, the layer is, so to speak, almost purely nervous in structure. A further peculiarity of the granule layer is one shared by adjacent layers, viz., an almost uniform character throughout the cerebellum. The several cell types, the fibers, and the characteristic acidophile structures of Denissenko form altogether a most complex-looking apparatus; but the complexity is a uniform complexity throughout the organ.

The most striking feature of the granule layer is doubtless the relative wealth of cells therein. There are few fixed tissues, barring tissues concerned with continuous generation of cells, elsewhere in the body which present so many nuclei to the unit of space. In the central nervous system itself, there are few loci which approach the granule layer in relative nuclear richness, excepting some parts of the limbic lobe and the stellate cell layers of the cerebral (particularly the calcarine) cortex. There is no good evidence of multiplication in the nerve elements of the granule layer, at any rate after early life.

Despite this general cell-wealth, the granule layer is notably lacking in neuroglia tissue, that is to say, in cells producing neuroglia fibrils, under normal conditions. This fact was observed by Weigert in 1895. The methods of Mallory

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and of Benda go far to confirm the point. This lack of neuroglia tissue in the granule layer is the more surprising when contrasted with the presence of considerable fibrillar substance, as demonstrated by the above methods, in adjacent layers. Thus the underlying white matter and the overlying Purkinje cell belt are well supplied with neuroglia fibrils, while the molecular layer still finds space among the branches of the Purkinje cell dendrites for a number of fibrils, even under normal conditions. The granule layer of the cerebellum may be logically grouped, therefore, with various peripheral nerve structures in the vertebrates, in its lack of neuroglia. This lack, however, is readily supplied under abnormal conditions.

Besides the relative cell wealth and (perhaps also relative) paucity of neuroglia tissue, the granule layer also shows a strikingly constant arrangement of the constituent elements, which holds not only throughout a given lamina but also, so far as known, throughout the cerebellar cortex. The cell arrangements, not merely of the granule layer, but also of the exterior layers, in the cerebellum are far more nearly uniform (or less differentiated ?) then the cell arrangements of the cerebral cortex. There is good ground for calling the cerebral cortex a composite of organs. So far, however, the cerebellum seems as uniform as it is complex. This fact has given rise from early days to the idea that the cerebellum acts as a unit. In any case, the granule layer is obviously a structural unit in the cerebellum.

What part shall be assigned to the granule layer in cerebellar activity? We might argue something of its functions from its situation between the core of white matter and the Purkinje cell belt. The presence of incoming and outgoing nerve fibers in the core of white matter obviously suggests that the activities of the cerebellar cortex complete an arc of impulses which flow in those fibers. It seems well established that the Purkinje cells are the locus of immediate origin for outgoing impulses. In case this is so, then the granule layer may probably serve, as seems likely from its site, as part of the centripetal mechanism.

As an example of the difficulties lodging herein, the hypothetical account of Kölliker, based on the work of Ramón y Cajal and others, may be cited. Kölliker (1896) regarded the Purkinje cells as the centrifugal elements, the moss fibers and climbing fibers (of the Golgi pictures) as the centripetal elements of the cerebellar cortex. Counting the Purkinje cells as the only centrifugal cells, it becomes hard to interrelate the remainder of the cells, classified by Kölliker as large and small granule cells, basket cells, and small cortical cells, which must all be related with the centripetal apparatus. Kölliker proposes that the moss fibers shall come into relation with the small and large granule cells, that the large granule cells shall be association cells, and that the small granule cells shall by means of their processes in the molecular layer come into relation with the Purkinje cell dendrites. This account leaves outstanding the basket cells and the small nerve cells of the cortex. Kölliker proposes that the climbing fibers and other centripetal fibers shall come into relation with these latter cells and these in turn with the Purkinje cell dendrites once more.

This account of Kölliker's yields some notion of the number of elements with which we deal. The account leaves out, moreover, the acidophile structures of Denissenko, which, as shown below, are remarkably resistant in disease.

Not to consider minutiæ at this point, it is evident that a true solution of these and kindred problems might be attained if we could differentially destroy the various elements in turn and watch the effect upon the activities of the apparatus in lower animals. A slower but perhaps surer method of attack might be to watch the effect of such differential or uncomplicated destruction of the various elements in man in the course of disease.

In default of a more rapid method of work, I have thought it profitable to look through a considerable number of cases, both with and without gross signs of cerebellar disease, to find what are the common lesions of the granule layer. An ulterior object was to arrange the elements of the granule layer in a series according to their resistance to injurious agents.

The present work is related to some previous work printed in 1905, where I described in some detail the characteristic lesions of the exterior layers in cases of marginal sclerosis in the human cerebellum. To these lesions there proved to be a rather obvious natural history. Thus the early lesions found in leptomeningitis (particularly tuberculous) could be aligned with the later lesions in local ischemia (well shown in infarctions of luetic origin). The series of changes thus made clear were used to explain the peculiar appearances — fibrillar overgrowth in three planes — in cases of stationary or terminal fibrillar gliosis. The first stage of this fibrillar gliosis in three planes was shown to be an overgrowth of the characteristic radial fibrils (Bergmann's fibers) of the molecular layer, an overgrowth frequently related with the death of Purkinje cells. The cells of origin for these radially shooting fibrils were found to be certain neuroglia cells in the Purkinje cell belt. In accord with the established conception of the Purkinje cells as the cells of least resistance in the cerebellum, it was found that the Purkinje cell belt is the locus of earliest activity in repair.

At present I wish to consider in a similar way the natural order of lesions in the inner (granule) layer of the human cerebellum. I have presented the cases on which the points are based in summary form. I have used various special methods on the material, but have depended for the general analysis of the findings in the granule layer upon various methods after fixation in Zenker's fluid, especially upon eosin and methylene blue, Mallory's aniline blue, and Mallory's phosphotungstic acid hematein methods, used on paraffine sections.

Case I. Case of defective girl, born without the use of instruments in the eighth month, one of twins (the other still-born). Slight evidence of consciousness or orientation (even for mother). General rigidity. Food given with difficulty. Constipation. Lived in cradle on its back. Convulsive seizures began after twentieth month. Death in thirty-seventh month from bronchopneumonia.*

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* For clinical history in full, see Bullard and Southard. A case of idiocy in a child with cystic hemispheres. Medical and Surgical Reports, Boston City Hospital, XV., 1905.

The autopsy showed gross cerebral changes. The ground plan of the cerebrum was preserved, but the substance of each hemisphere was largely replaced by a closed cystic cavity, independent of the ventricles. The interiors of the cystic cavities were traversed by delicate strands of neuroglia tissue. The pyramidal tracts had failed to develop.*

The cerebellum showed no reduction in size and possessed the usual markings.

The microscopic examination of the cerebellum in this case showed that the granule layer was far richer in cells, relatively to the unit of space, than the granule layer of the adult (see Plate IV., Figs. 1 and 2). The small cells called granule cells possess somewhat more vesicular nuclei than similar cells in the adult and are more closely packed together. The clear spaces between granule cell groups are more sharply marked off than in the adult and contain in some cases the characteristic acidophile structures of Denissenko. In other cases, however, the clear interspaces contain a nucleated structure in place of the non-nucleated structure of Denissenko. These structures, not seen in the adult, are spread not alone through the granule layer but also through the core of white fibers (where also they fail to occur in the adult). These cells have large homogeneous cell-bodies, rounded or oval in shape, and vary in size to above 60μ. They are supplied with single or sometimes with two rather dense central nuclei (see Plate IV., Fig. 3). There is no evidence from the tissues of this case that these cells produce neuroglia fibrils. It is still probable that they are cells of the interstitial or neuroglia series. It is not improbable that these cells in the granule layer may give rise to the acidophile structures of Denissenko. Of this, there is no proof, save that of suggestive situation and certain apparent transitions.

The case brings out the relatively even greater cell-wealth of the granule layer early in development and the occurrence or persistence of certain cells, probably neuroglia cells, which may be related with the development of the acidophile structures of Denissenko. The cell arrangements throughout the cerebellar cortex are uniform.

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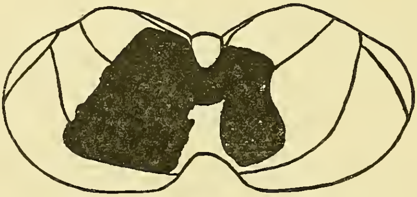
* For photographs showing cerebral aplasia of this case, see Bullard and Southard. Cystic aplasia of the cerebral hemispheres in an idiot child. Journ. Med. Research, XIV., 2, January, 1905.

CASE II. Epileptic imbecile of sixty-five years. One brother imbecile. Learned to walk at four or five. Never learned to speak beyond "yes" and "no," "papa" and "mamma," with a few oaths. Could make his wants known to family. Earned living by work on farm till fifty. Grew more childish and irritable later in life. Confused spells with hands raised to head at various times throughout life. Epileptic convulsions the last seven years of life. Occasionally noisy and homicidal. On admission, slight swaying in Romberg position. Knee-jerks dull, but equal. Other deep reflexes diminished. Superficial reflexes not obtained. Pupils small, oval perpendicularly, reacted within narrow limits. Petit mal and occasional severe epileptic convulsions during hospital stay (eight months). Death nine days after taking to bed with increased stupidity and signs of pneumonia in lower back.*

The autopsy † showed death due to typhoid fever and lobar pneumonia. The trunk showed little else abnormal, save half-sized testes, one containing a small cyst. There was coronary arteriosclerosis of moderate grade. The skull was symmetrical, the diploë congested. The pia mater was everywhere clear. The cerebrum showed anomalous fissuration, symmetrical in the anterior portions, both lateral and mesial, of both hemispheres. The affected lobes showed not only a microgyria with obscuring of normal markings, but also multiple fine corrugations of each gyrus with the thin pia mater exactly lining each irregularity.



The cerebellum showed an absence of lamination in a broad area over the upper surface (see text-figure). The parts without laminæ were the following: Anterior half of culmen monticuli, inner two-thirds of left lobus culminis, inner two-thirds of left lobus clivi, a narrow strip in the left lobus cacuminis posterior to the postclival fissure, inner third of right lobus culminus, inner third of right lobus clivi (with preservation of laminæ for a narrow strip anterior to postclival fissure). The clivus and the substance adjacent to the posterior cerebellar notch showed normal lamination.

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* Clinical notes through kindness of Dr. C. B. Sullivan, assistant physician to the Danvers Insane Hospital.

† Autopsy notes and cerebellum through kindness of Prof. A. M. Barrett of Ann Arbor, Mich., during whose service as pathologist to the Danvers Insane Hospital the case came to autopsy.

The microscopic examination of the non-laminated region of the cerebellum in this case showed interesting translocations of various structures. Isolated cells and groups of cells of the Purkinje cell type exhibit how little necessary relation exists between the development of Purkinje cells and that of the granule layer. Purkinje cells occasionally abut upon stray fascicles of white matter, as demonstrated in Weigert myelin sheath preparations.

The cell groups representing the granule layer are, as a rule, rounded like the normal granule layer, but occur in rather slender, anastomotic or isolated masses, as a rule, bordered by Purkinje cells (see Plate V., Fig. 4). There are occasional complete rings of cells, grouped to imitate the normal granule cells with cells of the Purkinje cell type both inside and outside the ring (see Plate V., Fig. 5). The cell-richness of these abnormal granule-cell accumulations is within normal limits. The acidophile structures of Denissenko are occasionally seen.

The molecular layer seems to be more irregular in development than the other layers and is subject to more sudden changes of contour. A layer roughly resembling the molecular layer invests the flat surface of the region affected and in some cases abuts directly upon fan-shaped masses of medullated fibers.

The case brings out the possible independence of development of the granule layer and the Purkinje cell belt (see Plate V., Fig. 6). In a case of severe early developmental injury, the general cell relations (possibly the general effectiveness of the apparatus) can be altered, yet the granule layer preserves independence as if it were to some degree a tissue unit.

Case III. C. K., salesman of forty-seven years, entered Dr. G. B. Shattuck's medical service at the Boston City Hospital Dec. 22, 1902. Alcoholic, obese. At thirty-seven in bed four to five weeks with rheumatic fever, at forty-one in bed four weeks with scarlet fever, at forty-three in bed eight weeks with broken leg.

Patient took to bed five days before entrance with weakness and anorexia.

On entrance apathetic, râles in lower right back, abdomen tympanitic, distended, Babinski reflex on both sides, leucocytes 20,000. Delirium next day, at first restless, later more quiet. Rose spots December 26th. December 28th difficult to rouse, quiet, numerous rose spots, fever, respiration rapid and difficult, leucocytes 8,800. Widal reaction absent. The râles increased, respiration became difficult, mucus could not be coughed up, cyanosis developed. Death eighth day after entrance, thirteenth day after symptoms developed.

The autopsy showed : Brain wt. 1,190 grams. Dura quite adherent to calvarium. Numerous pacchionian granulations along longitudinal sinus. Pia injected. Large amount of subpial fluid. Cortex soft and edematous. White matter normal. Lateral ventricles contain more fluid than normal. Lower portion of right hemisphere of cerebellum contains six or eight minute homorrhages, two of them extending into dentate nucleus.

Diagnoses. — Typhoid fever ; acute splenitis ; lymphnoditis (ileocecal group) ; acute bronchitis ; early pneumonia ; edema of cortex ; suppurative otitis media ; chronic interstitial orchitis.

The microscopic examination of the cerebellum in this case showed small hemorrhages into the molecular layer derived from small pial vessels, as a rule at the base of sulci. The molecular layer itself showed little reaction beyond slightly more vesicular nuclei in the neuroglia cells and pyknotic nerve-cell nuclei.

The reaction in the interior layers beyond the zone of destruction is striking see Plate VI., Figs. 7 and 8). For here, whether through pressure or poison, there is evidence of differential cell-destruction. Whereas the lamina as a whole is quite normal in cell supply, the region opposite the effusion of blood shows death of Purkinje cells and a sharply marked zone of granule cells with pyknotic nuclei. The acidophile structures of Denissenko are, however, not visibly altered.

The case is in effect a natural experiment to show that differential destruction of cellular elements occurs in the cerebellum and to give an idea of the order of cell destruction.

CASE IV. A poorly developed and ill-nourished male of twenty-five years. Never a bright scholar, mill worker. Albuminuria and defective memory three years before commitment, six years before death. Exaggerated knee-jerks, slow hesitant movements, complete disorientation, imperfect insight into condition, diminished effect. Hallucinations elicited two years after commitment. Death with unchanged signs.*

The microscopic examination of the cerebellum in this case showed the granule layer in numerous laminæ infiltrated with deposits of hyaline and lime salts (see Plate VII., Fig. 9). The granule cells are locally thinned out. The granule cells which remain are well preserved. There is a considerable supply of fibrillar neuroglia tissue throughout the laminæ both near the lime deposits and remote from any. Similar small lime deposits lie in the white matter near the granule layer. The acidophile structures of Denissenko are preserved.

CASE V. A. A., theater-employee of thirty-two, entered Dr. J. W. Bartol's service at the Boston City Hospital Aug. 25, 1905. The patient had been subject to diphtheria and scarlet fever in youth, besides "bilious" attacks followed by jaundice and vomiting. Gonorrhea. Syphilis denied. At twenty-eight the patient had an attack of headache, vertigo, nausea, and vomiting, lasting at least a fortnight. Two attacks afterward. All three were regarded as due to nephritis.

Four weeks before entrance (five weeks before death) occipital headache, vertigo, anorexia, pain in back, palpitation and dyspnea on exertion, cramps in feet at night, and increased amount of urine appeared. Gave up work eight days before entrance. Vomiting all one day four days before entrance.

On entrance, uremic odor to breath, systolic murmur in mitral region, marked arteriosclerosis, knee-jerks present and equal, spurious ankle-clonus. Convulsion lasting fifteen minutes the day following entrance. Swelling of eyelids. Twitching of head and arms. A swelling size of fist on right side of neck developed September 2. The patient became worse in the evening and died an hour later having developed considerable rigidity of neck, Kernig's sign, increase of knee-jerks, bilateral ankle-clonus.

The examination of the head † showed normal scalp, calvarium, and dura, well marked arachnoidal villi and basal vessels without gross sclerosis. Considerable subpial edema. Brain weight 1,435 grams. Substance uncommonly firm. Small cysts of choroid plexus. Pons, medulla, mid-brain, basal ganglia negative on section. Cerebellum showed nothing abnormal on section.

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* Clinical notes through the kindness of Dr. H. W. Mitchell, senior assistant physician to the Danvers Insane Hospital.

† I am obliged to Dr. C. W. Duval, pathologist to the Montreal General Hospital, for the tissues of this case, examined by him while assistant in pathology in the Boston City Hospital.

The aorta showed sclerosis without calcification. There were small old foci of calcification in the liver, and small calcareous masses in the pyramids of the kidneys. Chronic diffuse nephritis. Chronic splenitis. Death was due to acute purulent pericarditis.

The microscopic examination of the cerebellum in this case showed lesions similar to those of Case IV., but of severer character (see Plate VIII., Figs. 10 and 11). The acidophile structures remain intact. Numerous active fibril-producing astrocytes are found in the granule layer. The fibrils often embrace the acidophile structures closely, but apparently fail to pierce them (see Plate VIII., Fig. 11).

CASE VI. Undersized negro, of twenty-three years. Hutchinsonian teeth. Backward at school, of limited mental capacity. Tendency to fall down at play. Change for the worse asserted during last five or six years of life. Sold newspapers or blacked shoes up to within a year of death. In last months of life, showed general incoördination (coarse drunken movements) and tremors, with shifting gaze and tendency to nystagmus. Disorientation for time, place, and persons, confusion with coarsely relevant replies to questions, ill-defined and transitory delusions of persecution, auditory, visual, and tactile hallucinations, defective memory. A few remissions with slight clearing up of confusion.

The autopsy showed death due to an early bronchopneumonia (numerous staphylococci). The organs of the trunk were small and firm (heart, 130 grams; spleen, 25 grams; liver, 640 grams; kidneys together, 150 grams), and suggested, as did the brain, a hypoplasia. There was persistent thymus tissue in a tongued shaped mass, measuring 3×2×0.5 centimeters above the aortic arch. The femoral marrow was red and jelly-like, suggesting red bar-le-duc. The arch of the aorta showed a few plaques of sclerosis. The brain weighed 965 grams and showed chronic diffuse and focal leptomeningitis roughly corresponding with a diffuse cerebral and cerebellar gliosis. The cerebrum also showed focal sclerotic nodules, resembling those described in idiots by Bourneville, in the temporal gyri. Occipital microgyria. Gliotic lesions with pigmentation in posterior horns of spinal cord, perhaps related with a hydromyelia demonstrable at some levels.

The cerebellum was as firm as the normal olivary bodies. The hemispheres were symmetrical and of a normal appearance, save that the laminæ were slightly narrower than usual and very compactly set. The pia mater showed a diffuse haziness, best marked over the superior surface, besides focal thickenings of an unusual character, linear mounds of fibrous tissue running at an angle to the laminæ. There was no notable overgrowth of fibrous tissue at the base.

The microscopical examination showed in the cerebellar cortex the greatest possible gliosis consistent with maintenance of normal topography.

The meninges show an infiltration of moderate degree with cells of the lymphocyte series and pigment-bearing cells, together with edema over the most contracted lamellæ.

The vessels of the central white matter near the origins of the laminæ often show collections of granular material (possibly lime salts) ensheathing the intima. This process is less common in the meninges.

Some of the lamellæ have preserved a good number of Purkinje cells. Numerous marginal lamellæ show no Purkinje cells. Occasional Purkinje cells show two or more nuclei.

The molecular layer shows everywhere a notable increase in Bergmann's fibers, and in many lamellæ is diminished one-third or more in depth. A number of marginal lamellæ show a deep superficial zone of concentric fibrils in the locus of the fetal cell layer; this new layer is unevenly developed and recalls the (somewhat more richly cellular) focal superficial gliosis of the temporal cortex cerebri of the same case.

The granule layer shows a diffuse aplasia, and a thinning out of the granule cells, especially well shown toward the extremities of the lamellæ. The granule cells preserve in many places their usual grouping, but the picture gradually changes to one of granule cells of focal occurrence only or to one of complete loss of granule cells. The degree of fibrillary gliosis seems to parallel the loss of granule cells.

The white center shows a less dense gliosis (replacement gliosis) not in particular relation to vessels with occasional cystic deficiency near tips of laminæ.

Cerebellar cortex (myelin sheath stain). — In some cases almost total absence of fibers in centrum album gyrorum, in many cases pronounced thinning out toward the tip. A few fibers are almost everywhere preserved in the molecular layer. (Marchi) — Black granules, larger and less even in distribution in the centrum album than in the cerebral cortex by the same method.

Dentate nucleus. — High neuroglia fibril content about large nerve cells and notably within the nucleus (see especially phosphotungstic acid hematein preparations). The Marchi preparation shows large scattered drops particularly within nuclear limits.

I have been able to collect a few notes from the literature concerning the granule layer of the cerebellum in disease.

Bergmann,[1] 1861, described findings in an atrophic cerebellum, which, as Weigert has pointed out, are in part erroneous, since Bergmann regarded the radial fibers which now bear his name as forming a reticulum. Bergmann also described a paling-out of the granule layer and a diminution in number of granule cells.

Obersteiner,[2] 1871, described a focal lesion in the right cerebellar hemisphere in a man of thirty years dying of acute yellow atrophy of the liver. Obersteiner there called attention to the absence of Purkinje cells, to the development of numerous radial fibers in the molecular layer, and to a layer of concentric fibers (which he terms Ependymschicht) in the inner portion of the molecular layer. The Purkinje cell layer is figured as full of gaps and without cell accumulation. Obersteiner compares the granule layer to lymphoid tissue, remarking that the granule cells are held in a sponge-like ground substance. He found, also, in the granule layer a few larger elements which he regarded as degenerate nerve elements (one possessing two nuclei).

Kirchhoff,[3] 1882, described two cases of atrophy and sclerosis of the cerebellum, in a girl of seven (symptoms beginning at five years) and in an imbecile woman of twenty. Kirchhoff compared the appearance of the atrophic area in the superior vermis and left cerebellar hemisphere in the girl to the appearance of the embryonic cerebellum at the sixth month. Kirchhoff compared the condition of the more extensive cerebellar atrophy in the imbecile with the appearance of the embryonic cerebellum at the seventh month. In both cases Purkinje cells were absent from the atrophic areas. From the even diameters of the granule layer throughout the sclerotic laminæ in the imbecile, Kirchhoff argues the embryonic date and origin of the lesion. It is doubtful whether this argument can be upheld.

Sommer,[4] 1884, described cerebellar atrophy and sclerosis in a hydrocephalic of thirty years. He found the granule layer reduced from 300 to about 60μ in depth. The granule cells seemed normal but reduced in number and wide apart. In the area normally occupied by granule cells, Sommer found a granular ground substance in which are irregularly scattered many rounded nuclei. The small vessels had thickened walls. Sommer regarded these changes and those in the white matter as secondary to the absence of Purkinje cells and other alterations in the gray substance.

A. Meyer[5] (Osnabrück), 1890, figured diminution of nerve fibers in the cerebellar cortex, chiefly in cases of general paralysis, by means of Weigert's myelin sheath method. With respect to the other elements Meyer says that carmine preparations demonstrated no other alterations in the outer or in the granule layers, and believes that there is no alteration or numerical reduction in the Purkinje cells. He regarded the degeneration as primary and analogous to similar alterations in the cerebral cortex.

Weigert,[6] 1895, found "*so gut wie gar keine*" neuroglia fibers in the granule layer under normal conditions, and this in contrast with the Bergmann fibers of the molecular layer, the fibers surrounding the Purkinje cells, and the normally rich supply of fibers in the white matter. Weigert, however, mentions the increase of fibers in the granule layer in general paralysis and other conditions.

Raecke,[7] 1901, described an examination of the cerebellum in fifteen subjects of general paralysis by Weigert's neuroglia method. Raecke confirmed Weigert's observation of an increase of Bergmann's fibers in the molecular layer. Raecke found a peripheral zone of gliosis and a gliosis about the Purkinje cells. It is curious that the Purkinje cells, according to Raecke, show little or no change except in the severest foci, and Raecke is apparently of the opinion that the Purkinje cell alterations are secondary to the gliosis. The process in the granule layer was studied in the severest foci. Here the lost granule cells are simply replaced with neuroglia. Raecke goes on to say that — "since with every overgrowth of supportive tissue, whether primary or secondary, there must correspond a certain loss of nerve elements," it is probable that the earliest change in general paralysis affects the dendrites of the Purkinje cells.

INTERPRETATION OF FINDINGS. — The cerebellum is a good field for the study of differential lesions. There is a striking variety of structures in it. Yet this structural variety is, roughly speaking, the same throughout. The obvious structural unit is the cerebellar lamina. Each lamina presents a white core containing ingoing and outgoing fibers. Surrounding the white core is the gray matter of the cerebellar cortex. The elements of the cerebellar cortex comprise, (1) an important centrifugal apparatus — the Purkinje cells; and (2) a number of structures regarded as centripetal — the various structures of the granule layer, together with sundry elements of the molecular layer. The granule layer lies next to the white core and contains elements concerned presumably with the reception of impulses entering the lamina by way of the white core. The granule layer apparatus comes into relation with the manifold processes of the Purkinje cells which project into the molecular layer, in a fashion which is not obvious. The data of the Golgi impregnations here step in to demonstrate processes from the granule cells running outward to fall into relation with the dendrite forest of the molecular layer.

The course of a single impulse (an artificial abstraction in the cerebellum probably) might then be inward in a fiber of the white core to a granule cell, thence in a process to some dendrite of a Purkinje cell lying in the molecular layer, thence doubling on itself and running outward through the Purkinje cell and its single axis-cylinder to the white core again. It is of course doubtful whether any single impulse ever runs this uncomplicated course in the cerebellum. Not only have certain interposed elements been omitted in the series mentioned, but also it is highly probable that no single impulse goes far into the cerebellar cortex without starting up fresh impulses in several directions. The granule cell groups are precisely fitted for this, since little or no non-nervous material of the neuroglia type is discernible between the granule cells. Elsewhere in the cerebellum there are much more pronounced intervals between the nervous elements as well as a considerable supply of neuroglia which provides more effective surfaces of separation than the closely compact granule layer possesses.

Once running along Purkinje cell dendrites, it is difficult to see how a nerve impulse could be interrupted in its centrifugal course, although its intensity might conceivably depend upon the number of dendrites activated. If this conception be accurate, most of the transferent and inhibitory functions must be attributed to apparatus previously mentioned, namely, to apparatus centering in the granule layer.

Next to the granule cells the most prominent elements of the granule layer are the apparently homogeneous eosin staining structures of Denissenko. These are buffer elements imbedded in the anastomotic granule cell masses. Their functions may be to heighten, to depress, or otherwise to modify impulses which reach the granule layer. They may or may not alter in condition from moment to moment. It is possible, if improbable, that these eosin structures have no nervous function.

I have been studying the cerebellum, not so much in the hope of directly unfolding its functions, as to show what are the relative resistances of its elements to disease. In a previous paper I have described once more the familiar fact that the great elements of the Purkinje cell belt are the first to undergo destruction. I have also pointed out that in many types of lesion the Purkinje cell belt is the initial scene of activity, which activity takes the form of neuroglia cell overgrowth. When a lesion proceeds no farther than destruction of Purkinje cells, it is evident that the consequent alteration of function must be relatively coarse, tantamount perhaps to a mere suspension of functional discharge from the injured focus.

I have therefore looked over a number of cases to find examples of more exquisite injury to the centripetal or central apparatus, the apparatus which must have much to do with the coördination and perhaps with the inhibition of impulses. I have here presented a few cases to illustrate points of this nature. The most interesting result of this study is the observation that the eosin-staining structures of Denissenko are remarkably stable structures in comparison with the other elements of the granule layer.

The discovery of nucleated structures in place of the non-nucleated structures of Denissenko in a case of maldevelopment (Case I.) seems to offer hope that the development of these structures may be worked out. It is possible that the eosin structures of Denissenko stand in the same relation to nucleated structures in early life in which red blood globules stand to blasts. Work on this line is in progress.

The observation that Purkinje cells can develop independently of granule cells, and vice versa (Case II.), seems to be consistent with the conception of their functional independence outlined above. Granule cells appear to develop together and are supplied with the eosin structures of Denissenko.

A case of typhoid fever with small hemorrhages in the cerebellar pia mater (Case III.) offered a natural experiment in which both the maximum lability of the Purkinje cells and the initial neuroglia activity of the Purkinje cell belt are again demonstrated. The case likewise presented in the same region of focal atrophy necrosis of granule cells, among which however the eosin-staining structures of Denissenko persist.

Two further cases (Cases IV. and V.) demonstrated a curious deposition of hyaline material and lime salts confined largely to the granule layer. The lesion, of interest in itself, is here used to demonstrate the point that the eosin-staining structures persist despite the atrophy and death of numerous granule cells. In one case a delicate neuroglia overgrowth occurred, and the neuroglia fibrils are found embracing but not piercing the eosin-staining structures.

Work is in progress in the direction suggested by Case IV. Such a case demonstrates the possibility that, despite normal afferent nerves and a normal discharging apparatus (the Purkinje cells), there may be disorder of the most exquisite character in the central receptive apparatus (granule layer) of the cerebellum.

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DESCRIPTION OF PLATES.

PLATE IV.

FIGS. 1, 2, 3. — Cerebellum in Case I. (case of cystic aplasia of the cerebral hemispheres with absence of pyramidal tracts).

FIG 1. — Note the relative cell-richness of the granule layer. Compare with the normal cell supply of the granule layer as shown in Fig. 8.

FIG. 2. — Same case as Fig. 1. Granule layer showing supernormal cell-richness as compared with the adult. Note spaces between the granule cell clusters. Spaces contain single central nuclei.

FIG. 3 — Same case as Figs. 1 and 2. Large cells of white matter, one containing two nuclei and dark-staining central bodies. These cells are probably of the neuroglia series and possibly of the same type as those filling the clear spaces of the granule layer shown in Fig. 1 and particularly in Fig. 2.

PLATE V.

FIGS. 4, 5, 6. — Cerebellum in Case II. (Case of cerebellar anomaly: absence of lamination in part of superior surface of cerebellum in an epileptic imbecile).

FIG. 4 — Note irregular contours of tissue representing the granule layer. Heterotopia of Purkinje cells.

FIG. 5. — Heterotopia. Granule layer ring with Purkinje cells both inside and outside.

FIG. 6. — Group of Purkinje cells growing independently of the granule layer.

PLATE VI.

FIGS. 7, 8. — Cerebellum in Case III. (case of typhoid fever with small hemorrhages in the pia mater of the cerebellum). The two photographs are from the same lamina. Fig. 7 is taken from the injured side of the lamina, Fig. 8 from the uninjured side. The differences are due to the presence of a focus of pial hemorrhage opposite Fig. 7, absent opposite Fig. 8. The hemorrhage is not shown in Fig. 8, which exhibits its effects across the intervening molecular layer. Fig. 8 shows

1. Persistence of but one Purkinje cell, which was intensely eosinophilic and shows an eccentric nucleus;
2. Sparse and pyknotic granule cell nuclei in one focus adjacent to the Purkinje cell belt; and
3. Numerical increase of neuroglia cells in the Purkinje cell belt itself.

The lesions of Fig. 7 are shown nowhere else in the affected lamina or in adjacent laminæ. Fig. 8 shows essentially normal appearances.

PLATE VII.

FIG. 9. — Cerebellum in Case IV. (case regarded as dementia praecox). Lamina with coarse masses of lime, locally replacing groups of elements in the granule layer. Besides the large masses numerous smaller masses occur throughout the granule layer, and there is a diffuse delicate fibrillar gliosis throughout.

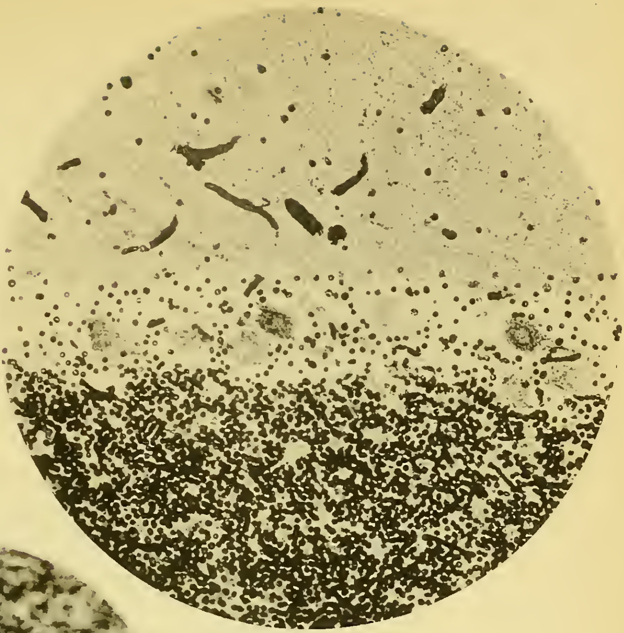
Plate VIII.

Figs. 10, 11. — Cerebellum in Case V. (case without nervous symptoms dying of acute purulent pericarditis. Foci of calcification found also in liver and kidneys). Compare Fig. 9. Marked atrophy of elements of granule layer. The granule cells preserve their arrangement in clusters. Small homogeneous apparently structureless bodies, slightly larger than granule cells, of a rounded or oval shape in section — structures (so-called "cells") of Denissenko — persist. Fig. 11 shows a swollen fibril-producing neuroglia cell. The fibrils stretch out to embrace a persistent structure of Denissenko.

Plate IX.

Figs. 12, 13. — Atrophy of granule cells with volume of layer largely maintained. Structures of Denissenko persist.

The Journal of Medical Research, Vol. XVI., No. 1, March, 1907.



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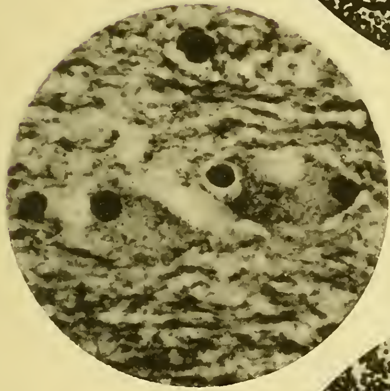

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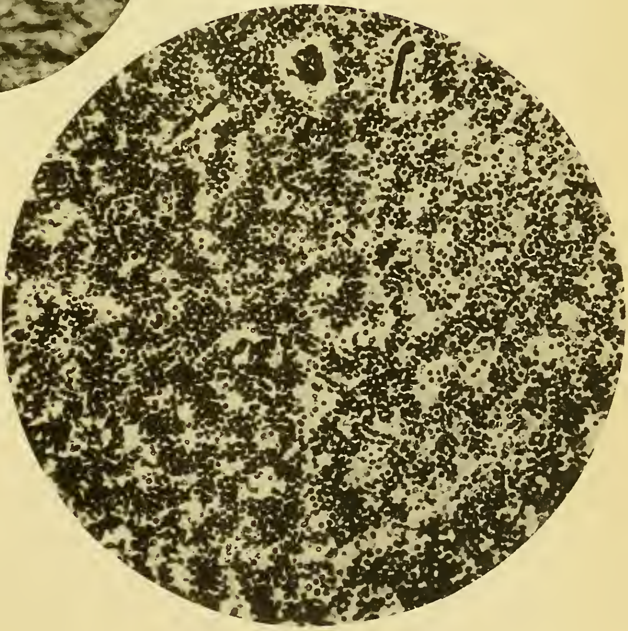

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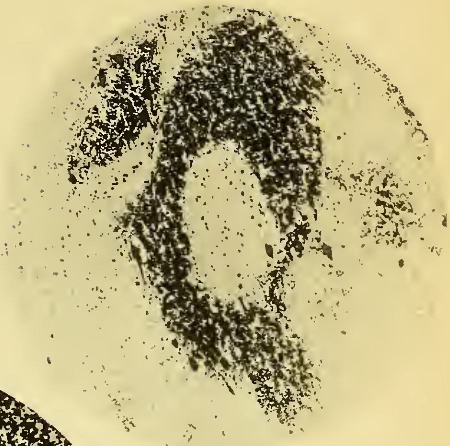
Southard

Cerebellum



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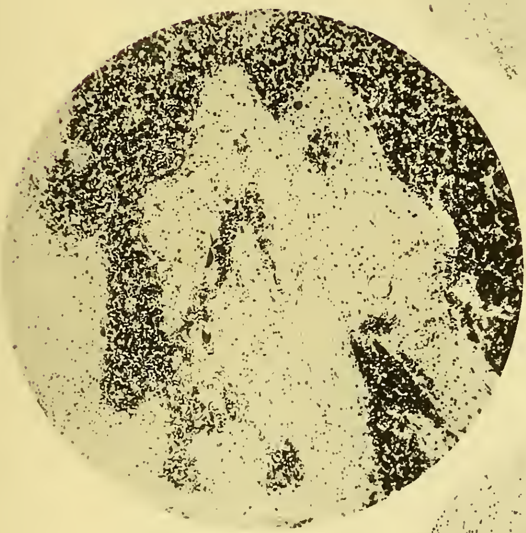

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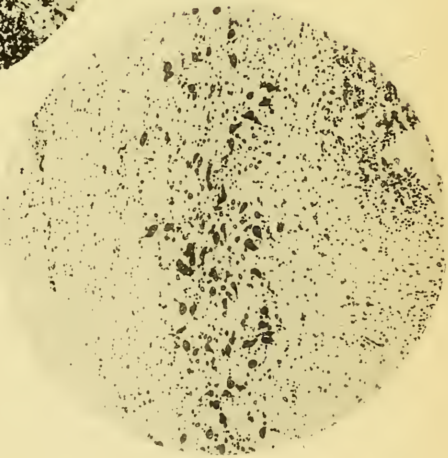

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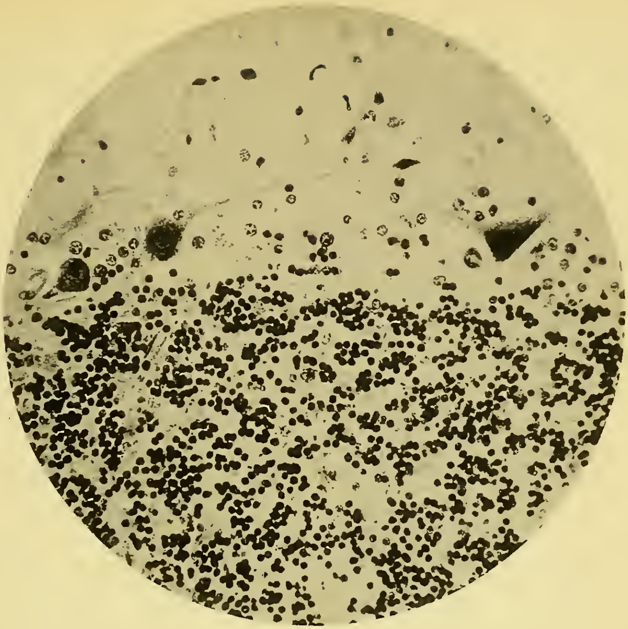

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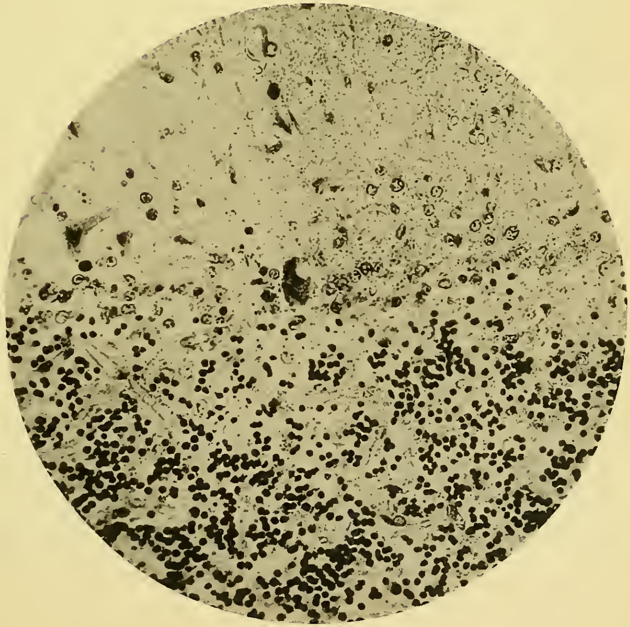

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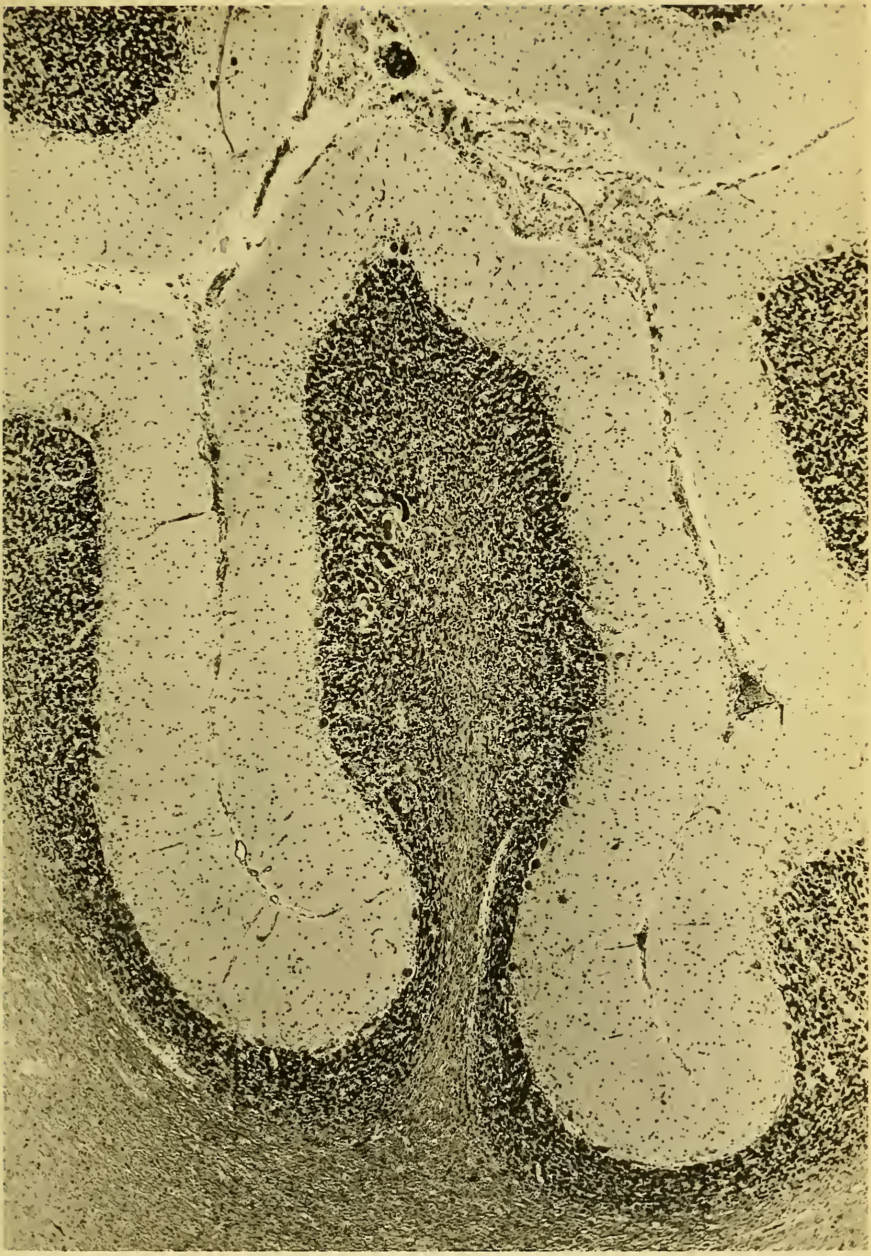

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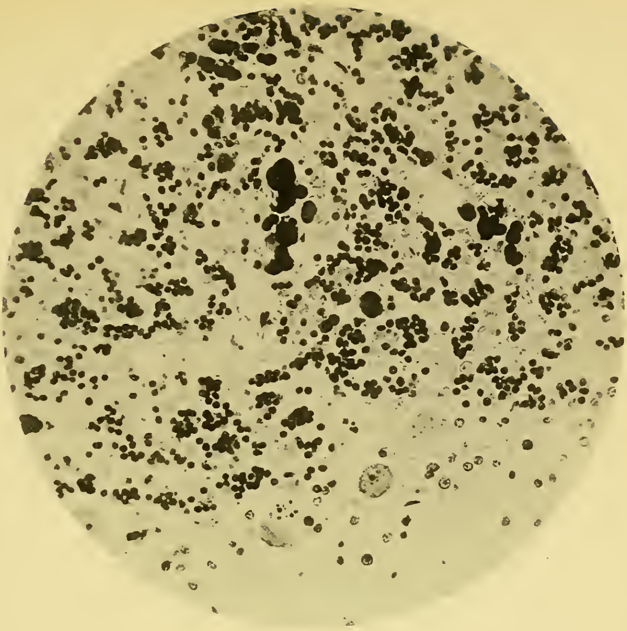

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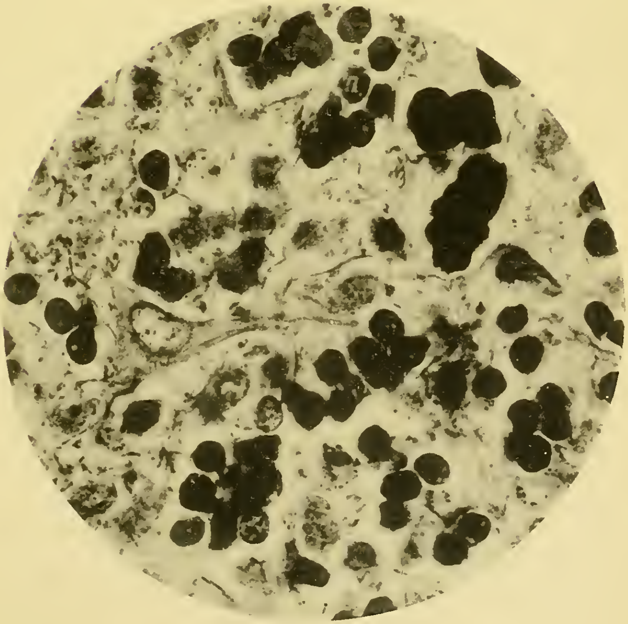

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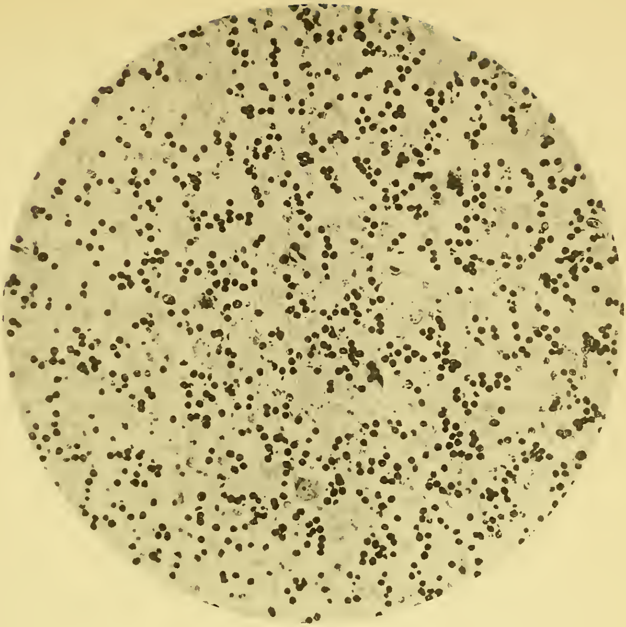

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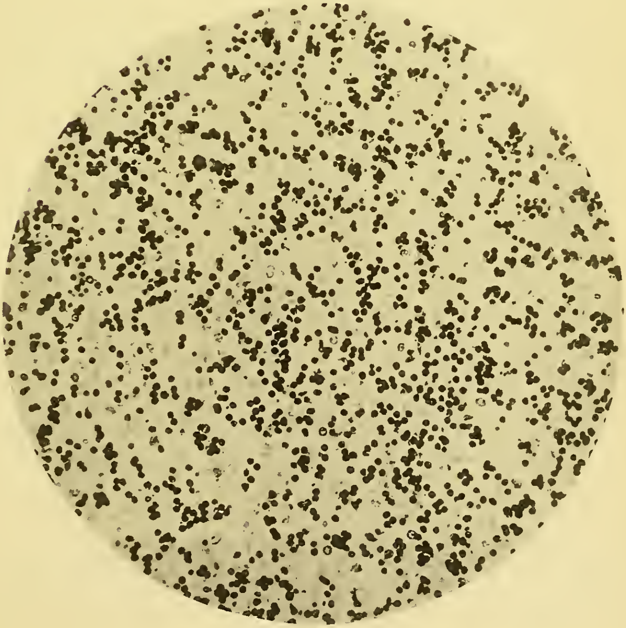

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Southard.

Cerebellum.

XI

NOTE ON CELL-FINDINGS IN SOFT BRAINS.[1]

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AND

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The present note calls attention to a point in pathological anatomy, viz., to the occasional occurrence at autopsy of brains and cords which are unduly soft to the feel, but have been subjected neither to edema nor to post mortem autolysis. Such reduction in consistence without increase of weight may be termed general encephalomalacia (myelomalacia). Some of the soft brains and cords show evidence of recent destruction of nerve fibers, demonstrable by familiar methods (Nissl's, Marchi's). The very diffuse malacia appears to be a phenomenon of terminal exhaustion and is perhaps related with such central neuritis (1) as may occur in Korsakoff's psychosis (2) and other conditions. The case of an epileptic dying at forty-two is given as paradigm of the condition.

Our attention was drawn to the condition in the course of work on accessible epilepsy tissues. Of course nowadays we very properly associate epilepsy rather with indurations of the brain than with encephalomalacia. As the appended case shows, however, the two conditions, focal sclerosis and general reduction in consistence without increase of weight, may be recognized together in the same subject It is even likely that focal glioses may stand out more prominently than usual in the soft brain and cord. Although recorded observations are not decisive on the point, it is not to be supposed that a large proportion of autopsied brains in epilepsy show malacia in this sense. We were surprised, however, to find that, out of a score of cases with soft brains (Danvers Insane Hospital series), a half-dozen proved (in the clinical records) epilepsy cases. But the histories failed to indicate that the encephalomalacia is directly related with epilepsy or with convulsions. Sometimes, as in the appended case, convulsions and other epileptic phenomena had ceased long before a terminal period of exhaustion, during which the lysis of nerve tissues had proceeded or begun. A review of the clinical histories in these cases pointed rather to a late, terminal, or agonal exhaustion than to any supposed convulsive constitution as the lytic agent. Some of the cases were febrile, others not, and some terminally febrile.

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[1] Read at the meeting of the American Association of Pathologists and Bacteriologists, Baltimore, 1906, and at the meeting of the New England Psychological Society at the Massachusetts Hospital for Epileptics, Palmer, 1906.

The general interpretation of such a finding is dubious. We are familiar with the general histolysis and swelling which follow shutting off the blood supply from a part of the brain (focal encephalomalacia with edema) and with the general softening down in situ of the brain after death (post mortem autolysis). The histology of these conditions differs from that of the general encephalomalacia under discussion. The soft brain (in the sense of this note) shows axonal reactions in nerve cells and Marchi degenerations in nerve fibers, which are of wide distribution and unequivocal as far as they go. The brain has been subjected not so much to a general histolysis as to a cytolysis or axonolysis. Although the effect produced is a general softening down of tissues, yet the lytic agent actually works differentially. This differential action is exemplified in the appended case, since the preserved nerve cells and nerve fibers within the sclerotic focus mentioned below show the same axonal reactions and Marchi degenerations as are shown by the cells and fibers of the brain at large. The neuroglial overgrowth is itself resistant to lysis but fails to protect the included nerve structures from lysis. This lytic change appears to be far more diffuse than any change which might underlie those changes in the second cortical layer of the brains of epileptics as first described by Bevan Lewis (3) or as described by Clark and Prout (4). It is to be observed, however, that Clark and Prout also mention chromatolysis in all types of cortical cell, most marked in the large pyramidal cells of the third layer. Bevan Lewis also notes the changes described by him as found to some degree in alcoholic brain-disease. The discovery of such changes both in and out of epilepsy makes clear how complex is the problem of the histology of epilepsy.

The practical recognition of this kind of brain and cord is important, because it would seem desirable for chemical pathology to begin upon work with cases showing such general disorder. Practically we are unable to draw many conclusions from the gross characters of brains examined very long post mortem. When the brain begins to stick to the knife on section, interpretation becomes difficult. Where post mortem changes can be excluded, there remain some sources of error. The chief source of error in the pathological diagnosis of soft brain would appear to be the occurrence of edema. The soft brain (in the sense of this note) is, however, not watery and fails to show the uneven cutting of gray and white matter, with tendency to bulging of the gray matter, which the edematous brain is apt to show. There seems also to be some evidence that a true terminal infectious encephalitis (of septicemic origin) is not infrequent; and we are not yet familiar with the possible effects of this upon nerve tissues. It is obvious that any or all of these softening agents may be combined. It is true also that a gliotic brain might not reveal to the fingers as much about injuries to the included fibers as would a brain of normal framework. It is possible that post mortem lysis proceeds with increased speed where a softening process has already begun ante mortem. The brain of encephalomalacia characteristically fails to show the increase of weight which is shown by edematous brains. Where brains are under weight at the outset, there is no good standard for determining the possible effect of the lytic changes on weight.

Following are the findings in a case chosen to illustrate the condition:

CLINICAL HISTORY.[2]

A. H., negress, age 42, was committed to the Danvers Insane Hospital July 14, 1902, discharged November 10, 1904, recommitted January 17, 1906, and discharged dead March 19, 1906, being under observation thus about thirty months.

Family History.—Incomplete; father died at 84; mother, of consumption at 54.

Personal History.—Woman of ordinary mental capacity. Characteristic epileptic attacks (unconsciousness, foaming at the mouth, biting of tongue, twitching) began eight or ten years before admission. The convulsions came every day or two for a month. She was "cured" of these at a hospital. Convulsions recurred three years before admission to Danvers, and came every month or two months. Before admission the patient had four fits and became thereafter dull and stupid, later disturbed and noisy. Both eyes were prominent, the left more than the right. Moderate external strabismus of left eye. Vision good. Was able to read. Ophthalmoscopic examination showed dilated and tortuous veins. Pupils equal, reacted to light. Knee-jerks equal, normal. Romberg's sign absent. The urine showed a trace of albumin.

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[2] Abstract made from the clinical records of Drs. H. A. Cotton and E. E. Bessey, assistant physicians to the Danvers Insane Hospital.

At admission: Inattentive, confused, talkative, hesitant in answering questions, pronouncing test phrases poorly and calculating poorly. Improvement for two weeks. July 31, three convulsions, followed by resistivism, confusion, vertigo, more unsteady gait, and headache. Cleared up in a few weeks and became an efficient ward helper, having three or four convulsions in a month, ushered in by a cry, followed by stupor for two hours or more. In February and March, 1903, severe headache with shooting pains in left temporal region, later over frontal region. Darting pains in right temporal region. Right pupil larger than left, very slow direct light reflex and slow consensual light reflex in right pupil. Left knee-jerk livelier than right. Clonus absent. Tongue slightly protruded to left.

April 6, convulsions, lasting two minutes. Head and eyes turned to left with twitching. Left hand held rigid. Right hand convulsed.

Discharged in 1904, improved. Orientation usually fair, memory good, insight into condition good, exophthalmos not so marked, considerable headache.

Readmitted January 17, 1906, weighing about twenty-five pounds less than at first admission and too weak to walk without support. External strabismus of left eye. Protrusion of both eyes, notably of left. Right pupil larger than left. Left knee-jerk brisker than right. Hebetude. Impairment of memory. Recognized persons, but failed to recall names. No spontaneous talk. On being aroused, said, "I don't know," or answered by "yes" or "no." Untidy. A few convulsions observed by nurse, lasting a few minutes, with eyes rolled upwards, head turned to the left, arms rigid, and a slight frothing at mouth.

Steady decline till death. Occasional slight convulsions. Expressions of fear or terrified looks. Confused, noisy, rolling about in bed. Conjunctivitis, and hypopyon of left eye. Stupor from which she can be aroused. Abdomen distended. Constipation. Difficulty in swallowing. Coma for twenty-four hours before death.

Anatomical Findings.

Autopsy eleven hours after death by E. E. Southard. Following are the findings in the head, together with the anatomical diagnoses:

Head.—Scalp edematous anteriorly. Calvarium thick, with little diploe. Dura adherent to calvarium in bregmatic region. Sinuses normal. Pia mater edematous, without notable thickenings. Brain weight, 1055 gms. Substance remarkably and evenly reduced in consistence in both white and gray matter. Olives and dentate nuclei as soft as normal cortex cerebri. The appearances resemble those of many days post mortem. The central convolution of the right hemisphere is much firmer than the surrounding convolutions. The right ascending frontal convolution is firm throughout the arm area and for a portion of the face and leg areas. The right ascending parietal convolution is equally firm for a like distance. The sclerosis is sharply marked off by sulci, by the postcentral sulci behind (so as to exclude the superior parietal and supramarginal regions) and by the anterior ramus of the inferior precentral sulcus and the superior frontal sulcus in front and above (so as to exclude the greater part of the middle frontal and the superior frontal gyri.) There is no demonstrable atrophy or chronic pial reaction in relation with the sclerosis. The white matter beneath presents no change except the universal reduction in consistence.

Cord.—Numerous calcified plaques in posterior lumbar pia.

Middle Ears.—Left middle ear contains semi-liquid pus. *Retinæ* removed from behind show left nerve-head reduced, about one-third in surface area. Vessels injected. *Marrow* of femur fatty.

ANATOMICAL DIAGNOSIS.

Encephalomalacia and myelomalacia.

Early bronchopneumonia, left lower lobe.

Sclerosis of middle two-thirds of right central convolutions and posterior part of right middle frontal convolution.

Atrophy of left optic nerve.

Conjunctivitis, keratitis, and hypopyon of left eye.

Left ophthalmoptosis.

General arteriosclerosis (aortic, coronary).

Slight mitral sclerosis.

Old infarct of kidney.

Chronic external adhesive pachymeningitis.

Chronic adhesive pleuritis.

Chronic focal adhesive pericarditis.

Mural and subperitoneal fibromyomata of uterus.

MICROSCOPIC FINDINGS.

Sections from seven regions in each hemisphere were examined by Nissl's method, together with several regions of the cerebellum and various levels of the spinal cord. Sections from adjacent regions were stained by Weigert's myelin sheath stain and impregnated by the method of Marchi for fat.

The details of the microscopic work are reserved for a later comparative study of this and similar cases. The finding common to all parts of the central nervous system examined was the axonal reaction of Nissl, with characteristic eccentricity of nucleus and solution of cytoplasmic bodies, in countless examples of those cell types in which this reaction can be made out. A closely similar change occurred in many of the Purkinje cells of the cerebellum; a large proportion of the horn cells of the spinal cord show the reaction in classical fashion. The Marchi reaction was appropriately diffuse. The number of fibers affected would suggest that far more cells of origin are affected than can be demonstrated as injured by the Nissl method.

REMARKS.

The anatomist is prone to neglect the general feel of the brain and cord at autopsy. He is familiar enough with focal alterations of consistence; thus, with foci of induration (scars, focal glioses) and with foci of subnormal consistence (focal encephalomalacia, focal encephalitis). A state of general induration is recognized as due to diffuse fibrillar gliosis. General reduction of consistence is least easy to interpret.

The plastic softness and swelling of edematous brains may be told from the diffluence of brains as autolyzed post mortem. We have here noted a condition of general encephalomalacia which we take to be of ante mortem origin, though doubtless it is speedily emphasized by post mortem changes.

The soft brains and soft cords of this group are not produced by vascular lesions and, unlike edematous organs, show no essential increase of volume or weight. This type of general encephalomalacia (myelomalacia) seems not unlike the state of the brain and cord after post mortem autolysis and is possibly due to a similar process.

Although the process has the appearance of a general histolysis, yet histological study shows that the lysis is essentially differential (diffuse axonal reactions in nerve cells and still more diffuse Marchi degenerations). Where, as in the illustrative case, a focal induration also occurs, the histolysis is readily seen to be differential because the nerve cells and fibers which still live in the sclerotic focus are subject to the same cytolyses (axonolyses) as are the cells and fibers of the brain at large. What the lytic agent is remains obscure.

General encephalomalacia (myelomalacia, neuromalacia?) is clinically related with a late, terminal, or agonal exhaustion and is sometimes seen following epilepsy as well as in other conditions.

LITERATURE.

(1) A. Meyer: "Parenchymatous Systemic Degenerations." Brain. XXIV, 1901, p. 47.
(2) F. R. Sims: "Anatomical Changes in Two Cases of Korsakoff's Psychosis." Journ. Nerv. Ment. Dis., vol. 32, 1905, p. 160.
(3) Bevan Lewis: "Text-book of Mental Diseases," 1890, pp. 522-8.
(4) Clark and Prout: "Status Epilepticus." American Journal of Insanity, October, 1903.

XII

GLIOTIC CYST OF THE RIGHT SUPERIOR PARIETAL LOBULE.

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We wish to present a case of cerebral disorder in a young woman. The case ran a course of six years with general and focal symptoms and ended in death at the age of thirty-two. Two years after the onset of symptoms the skull was trephined over the right ascending parietal convolution at a point just anterior to the focal lesion found at autopsy four years later. This lesion was a cyst, 2.5 cm. in diameter, bounded internally by the ependyma of the lateral ventricle, externally by fibrous tissue continuous with the thickened and dimpled pia mater. On all other sides it was bounded by a zone of gliosis. The nature and origin of the cyst are in question. The condition may be classified perhaps as one of porencephaly. To avoid various connotations, we have called the condition gliotic cyst.

I. CLINICAL HISTORY.

An unmarried nurse of 28, after two years of severe parietal headaches accompanied by occasional vomiting and by impairment of vision, was admitted to the Boston City Hospital, January 1, 1894. Just before entrance she had suffered marked loss of power in left hand, arm, and leg, and the headaches had become intensified. Thermal, tactile, and muscular sense remained normal. The reflexes were unaltered.

On January 7 the right arm was somewhat improved, and she could walk with a hesitating gait. The headaches continued, and there was marked photophobia.

On March 25, after about eleven weeks of variable short periods of improvement and relapse, she was recommended to the surgical side for trephining. An aural examination before operation was reported negative. The skull was trephined by Dr.

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[1] Working in the fourth year elective in Neuropathology in the Harvard Medical School, 1905-1906.

E. H. Bradford just over the upper part of the fissure of Rolando. Some thinning of the skull at the point of trephine was noted. The dura bulged markedly. Pulsation was visible. The meninges were adherent to the inner table at one small spot. Nothing further was discovered.

The headaches returned on the third day after operation. On June 4, 1894, she was discharged only slightly relieved to the Convalescent Home where she remained until May 13, 1898, about four years. In the interim she had become completely blind. On May 13 she was admitted to the surgical side with a provisional diagnosis of general peritonitis. Operation the same day showed the entire length of the small intestine to be lifeless and black. The patient died in the afternoon.

II. FINDINGS AT AUTOPSY.

Autopsy the following day, by Dr. F. B. Mallory, showed thrombosis of the portal vein and its branches, infarction of the small intestine and multiple infarctions of the spleen. The brain showed, just back of the right postcentral convolution, a depressed area, greyish and rather fibrous in appearance. A frontal section through this point revealed an irregular stringy mass of rather dense fibrous looking tissue. This mass formed part of a wall of a cyst 2.5 cm. in diameter. The cyst reached to the right lateral ventricle and was only separated from the latter by the ependymal lining. The fibrous looking tissue projected in bands in all directions throughout the cyst and seemed to form a more or less intimate part of it. In other words the fibrous looking tissue did not form the wall of the cyst, but rather was included and extended in all directions therein, being limited peripherally by brain tissue only and not by a definite capsule or wall. No other lesions were found in the brain.

III. MICROSCOPIC EXAMINATION.

The microscopic examination was made largely to determine the cellular structure and pathogenesis of the cystic lesion in the right superior parietal lobule. It seemed possible to align this condition of gliotic cyst in the cerebral gray and white matter with the familiar condition of syringomyelia in the spinal cord. Syringomyelia in advanced cases can be faithfully described as a condition of gliotic cyst of the posterior horn and adjacent white matter. The present case showed a gliotic cyst of unknown duration (cerebral symptoms six years) involving gray and white matter of the cerebrum in an area which modern work has shown to be sensory in function.

Sections for microscopic study were taken to show tissue immediately surrounding the cyst, and the nature of its interior surface.

Four processes of staining were employed, *i. e.,* (1) Mallory's phosphotungstic acid-hematoxylin stain; (2) Mallory's anilin-blue stain for the intercellular connective-tissue fibrils; (3) alum-hematoxylin and eosin stain, and (4) Weigert's stain for myelin sheaths.

Microscopic examinations of these sections revealed the following: An absence of vascular lesions, an absence of phagocytic cells in the walls of blood vessels and of the cyst; some cellular and fibrillar gliosis in the subependymal region; an occasional tremendous spider-cell lying in the subependymal neuroglia; considerable fibrillar gliosis between the bundles of myelinated fibres; an absence of demonstrable neuroglia changes in the adjacent cortex as well as absence of subpial gliosis.

IV. REMARKS.

We have to deal in the present case with a condition of cyst with gliosis in the right superior parietal lobule. The cyst was 2.5 cm. in diameter and did not communicate with the lateral ventricle. The origin of the cyst comes in question.

We are able to do no more perhaps than enumerate possibilities.

Without reference to the subject's history, we might propose that this condition of gliotic cyst could be labelled anatomically as follows:

1. *Agenesia,* defining a condition in which the original tissue had never been deposited in embryonic life.

2. *Aplasia,* defining a condition in which the original elements laid down in this focus failed to develop for some reason.

3. *Necrosis* of focal character, defining a condition in which the necrotizing agent destroyed cells which had normally developed. Under this head might be considered:

(a) Infarction of embolic or thrombotic origin.

(b) Hemorrhage with absorption and incomplete repair.

(c) Abscess, turbercle, gumma, or other infective lesion, followed by absorption of disease products without adequate replacement with scar-tissue or gliosis.

(d) Echinococcus disease.

4. *Tumor* formation with cystic degeneration (cystic glioma or gliosis with cyst formation).

The history of the subject fails to support several of the possibilities mentioned and indeed seems inconsistent with a number of them. Perhaps the earliest symptoms were due more to heightened intracranial pressure than to the focal lesion. The greater emphasis at times of right parietal headache might be ascribed to the focal lesion. In any event the results of the focal lesion and the results of the consequent increase of intracranial pressure can hardly be separated clinically at this time.

The woman had been perfectly normal up to the onset of her disease six years before death. She had been a capable trained nurse. Clinically there could be no suspicion of maldevelopment, or of any form of bacterial or parasitic infection.

Disregarding the clinical data for the time being, we are in a position to exclude the likelihood of most of the possible conditions mentioned above. The absence of vessel lesions and of phagocytic cells is striking. The normal character of tissues a few millimeters distant from the gliotic wall of the cyst is suggestive of an acquired, rather than of a congenital, lesion.

We have thought it worth while to present the case as a phenomenon to be explained. No explanation seems so satisfactory as that of glioma with cystic degeneration. This diagnosis fails, however, to explain much, since the significance, both of glioma and of cystic degeneration, remains unclear. The best suggestion we can offer is that the condition is analogous to syringomyelia. Gliotic cysts of the cerebrum will be understood when syringomyelia is understood. Both conditions depend for their explanation upon the theory of neuroglia changes. Let the nerve tissues of a part of the superior parietal lobule in this case undergo a slow death like that in the tissues of the posterior horn of the spinal cord in a case of syringomyelia. Vascular lesions fail to ensue. The neuroglia attempts to fulfil the function usually attributed to it—replacement-gliosis. The attempt is a failure, as in the banal condition of cerebral infarction, and a condition grossly resembling a cyst of softening follows. Alterations in the amount of enclosed liquid ensue, just as in syringomyelia, and effect alterations of symptoms, complicated, however, to an extent not possible in syringomyelia, by heightened intracranial pressure.

Just as in syringomyelia, it is perhaps not possible to allege that the destruction of nerve elements in the area which afterwards becomes cystic is a primary or direct destruction of nerve elements. Is it possible that the gliosis is primary and not wholly a replacement-gliosis?

Further cases may determine whether there is a cerebral disease which proceeds on the lines of syringomyelia.

DESCRIPTION OF FIGURES.

FIG. 1.—Photograph of gliotic cyst, abutting on ventricle.

FIG. 2.—To show situation of cyst. Dotted lines are to represent dilatation of ventricles.

Sagittal section of right hemisphere taken 2.7 cm. from median line.

Dejerine, Anatomie des Centres Nerveux, 1895, Vol. I.

F_2, second frontal convolution. *FA*, ascending frontal convolution. *R*, fissure of Rolando. *PA*, ascending parietal convolution. O_2, second occipital convolution. *LN*, part of lenticular nucleus. *IC*, part of internal capsule. *V*, occipital horn of lateral ventricle.

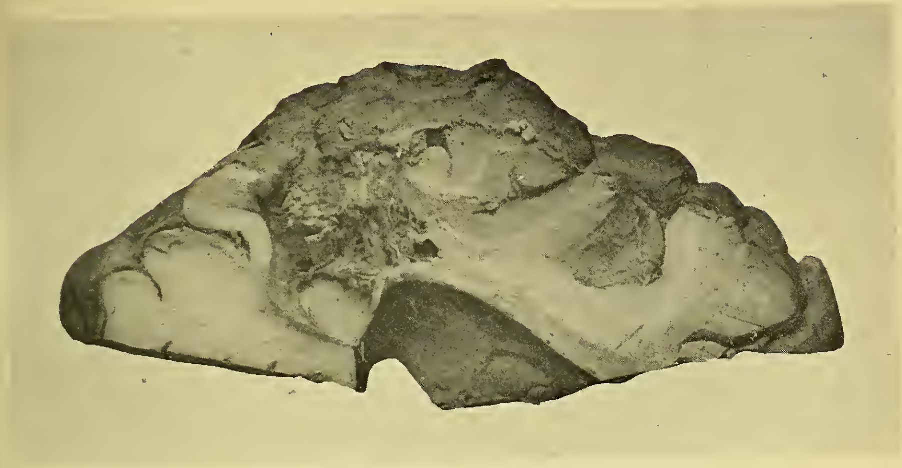

FIG. 1.

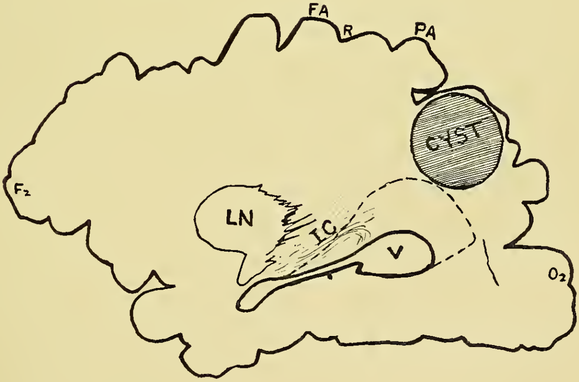

FIG. 2.

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Diffuse and Focal Lesions in a Case of late Epilepsy.

1908

DIFFUSE AND FOCAL LESIONS IN A CASE OF LATE EPILEPSY.

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The present case of late epilepsy yielded a multiplicity of lesions. Several of these lesions, as well as several combinations of them, might plausibly account for (or be ascribed to) the epilepsy.

The epilepsy was of fifteen years' standing, with death at the age of sixty-six. The most striking feature of the case was a focus of softening in the left cerebellar hemisphere. There were diffuse lesions of the rest of the nervous system, among them pigmentation with a tendency to affect certain cortical cell layers, perivascular gliosis notably of the spinal cord, and superficial focal glioses affecting the subpial layer in numerous regions of the cerebrum and the spinal cord. These latter focal glioses appear to have much in common with the "granules" of granular ependymitis, with which, in the hippocampal region of the present case, they are associated.

Workers in the field of epilepsy tend to exclude from study cases in which organic basis is assumed—such lesions being generally thought to be in the cerebral cortex. Experimental work has for years called attention to other possible sources of convulsions. The cerebellum should not be neglected in the study of the "Epileptogenous" areas. If the focal lesions of the cerebrum in such cases are regarded as causes or effects of epilepsy, then the occurrence of similar lesions in the spinal cord must also be taken into account.

CLINICAL HISTORY:

An Irish woman of sixty-three years was committed to the Danvers Insane Hospital, April 3, 1903, and died there August 31, 1906. On the night of admission she had a convulsive seizure and remained subject to such seizures at irregular intervals until the day of her death. She was subject to cardio-renal "ups and downs" and succumbed to an infection of the lower bowel.

On admission the patient showed general arteriosclerosis, (notably brachial and temporal), enlarged heart, varicose veins and ulcer of left leg, slight general anasarca, albuminuria and cylindruria. There were small pitted scars on the chest and a large scar at the angle of right scapula. Gait feeble, knee-jerks equal and diminished, extreme deafness Memory impaired for remote as well as recent events. Memory defect appreciated by patient. Dull and sleepy.

The patient injured her forehead and face in her seizure the first night and had a slight fever thereafter. She grew better of this The albumin and cast disappeared from the urine within three weeks of entrance. She remained for the most part quiet and became tidy, was as a rule agreeable though variable in mood, and gradually became partially oriented for time, place, and for some persons.

A second seizure occurred early in May, 1903. July 22, she was irritable all day and had two general convulsions that night.--She denied the convulsions next day. During the years following she would remain for the most part quiet and contented, gradually losing her orientation for time and becoming quite disoriented for place and person. Before and after her convulsions she was irritable. Later she would become confused after the seizures were over. She had occasional periods of weakness which confined her to bed. These periods followed the convulsions as a rule. At one time fever and signs in the lungs developed; but from these she made recovery.

The convulsions were general in character and are described, in 1906, as lasting ten to fifteen minutes, followed by stupor lasting several hours. Both arms and both legs moved. There was internal movement of the lower jaw; but no frothing at the mouth was observed. The eyes were closed. There was incontinence of urine and at times feces.

The terminal illness was ushered in by complaint of general weakness and several convulsions. Diarrhoea followed, and mucus and blood occurred in dejects on the fourth day. Death three days later. Convulsive movements of abdominal muscles an hour before death.*

FINDINGS AT AUTOPSY.

The autopsy was performed four hours post mortem. (E. E. S.) Head, cord and trunk were examined. A description of the head findings, together with an abstract of the other findings, follows:

(*I am indebted for the use of this history to Dr. W. P. Mitchell, Assistant Physician to the Danvers Insane Hospital.)

Head:—Hair, gray, fairly thick. Scalp, normal. Calvarium heavy and dense. Inner table of frontal bone raised in low smooth rounds, with which the dura mater has inseparably fused. Dura mater firmly attached to calvarium in bregmatic region and a long saggital suture. Dural sinuses contain suror clot. Arachnoidal villi in moderate amount. Pia mater of a normal appearance, contains little or no liquid over vertex. The basal cisternae contain considerable liquid. The basal vessels show a trifling amount of diffuse sclerotic thickening. Brain:—Weight, 1165 gms. Substance everywhere firmer than normal except over the right flank, which is softer than normal in the lower two-thirds of the central convolutions and the adjacent part of first temporal convolution. This soft part suggests plugging of associated vessels, but no vascular lesion was discovered on minute dissection. The section surfaces of the cerebral hemispheres are of a normal appearance, except that the white matter is more easily crushed under the soft place in the right hemisphere. The hippocampal gyri are not firmer than the rest of the brain. The brain was searched minutely for lesions which could be associated with epilepsy and sectioned throughout at intervals of 2mm. No lesion was found within the cranium except in the left hemisphere of the cerebellum. The substance of the left lobus clivi (lobus lunatus posterior) and the adjacent pia mater and opposite face of the postclival fissure (a thin strip of the left lobus cacuminis (lobus postero-superior), contain, at a point 3 cm. to left of median line and 1.5 cm. anterior to posterior border of cerebellum, a focal lesion of lenticular shape, measuring 1x1x0.6 cm., with the flat faces tilting backward, upward, and slightly outward parallel with the plane of the postclival fissure. The lesion is cyst, a softening with coffee-jelly-like contents, shot through by vascular threads. There is no grossly evident zone of reaction about the lesion, which abuts directly upon the white matter of the lobus lunatus posterior and upon the main mass of cerebellar white matter, but has involved a part only of the cortex of the postero-superior lobe.

ANATOMICAL FINDINGS.

Acute ileitis, colitis, proctitis, with early serous exudate in peritoneum.

Acute vegetative aortic endocarditis.

Acute encephalitis (right central and first temporal gyri).

General arteriosclerosis (aortic, coronary, basal)

Mitral sclerosis.

Chronic fibrous myocarditis.

Brown atrophy of heart muscle.

Chronic diffuse nephritis with cysts.

Edema of ankles.

Slight emphysema of lungs.

Chronic gastritis.

Chronic adhesive pleuritis.

Chronic perityphlitis.

Chronic osteitis. (inner table of frontal bone).

Chronic external adhesive pachymeningitis.

Cerebral gliosis.

Small cyst of softening about left postclival fissure of cerebellum.

MICROSCOPIC FINDINGS.

Plates were made from the heart's blood, from the cerebrospinal fluid by way of the infundibulum, and from the left inferior frontal gyrus. The heart's blood showed staphylococcus pyogenes albus. The cerebrospinal fluid showed staphylococcus pyogenes aureus and a bacillus of the ambiguous group. The left inferior frontal gyrus was sterile. (Dr. F. P. Gay, Bacteriologist of the Danvers Insane Hospital).

The heart shows a moderate accumulation of perinuclear pigment in the great majority of fibers, a variable amount of fibrous thickening as a rule of interfascicular distribution, a moderate degree of sclerosis in some of the small coronary branches, and a trifling amount of subepicardial focal accumulation of mononuclear cells.

The lung shows, besides emphysema, a moderate number of phagocytic mononuclear cells in the alveoli. There is relatively more intense arteriosclerosis than in the heart. A mural thrombus with partial organization in one large artery failed to produce infarction.

The spleen shows chronic passive congestion of moderate degree. Extensive hyaline changes affect the walls of almost all the arteries. Small hemorrhages in pulp. Arteriosclerosis.

The liver shows a trivial amount of portal cirrhosis with an occasional focus of fibrosis and pigmented cells replacing some part of the lobule, as a rule nearer the portal tissue than the central veins. Slight chronic passive congestion.

The kidneys shows a variable amount of chronic interstitial overgrowth (in places extensive) a moderate degree of arteriosclerosis, and very numerous casts in the tubules.

The thyroid shows moderate arteriosclerosis and in places a voluminous accumulation of mononuclear cells about colloid, containing tubules. The majority of acini are free from these cells.

The pituitary body shows in the glandular part an unusual amount of colloid and a high proportion of eosinophile gland cells. One focus of maximal eosinophilia measures 2 mm. in diameter and lies about 2 mm. from the junction of the two portions.

The nerve cells of the gasserian ganglia are often pigmented. The pigment is often adjacent to the nuclei, but is sometimes found in the more usual peripheral site.

The spinal cord shows a heavy neuroglia framework throughout, as demonstrated by Mallory's phosphotungstic acid and hematein method after Zenker's fixation. The framework is particularly heavy in the subpial region of the posterior columns and in the vascular processes setting in therefrom. The subpial gliosis is best marked in sections taken from the lumbar region, where processes of glia make out in small promontories into the pia mater overlying the lateral columns. The interior of the cord shows the most marked fibrillar overgrowth about the central canal and along the edges of the gray matter adjacent to the posterior columns. The gliosis about the small vessels of the posterior columns is striking. The perivascular gliosis is best marked in the middle portions of the columns of Goll in the thoracic cord.

Axonal reactions cannot be demonstrated in the nerve cells of three segments of the spinal cord fixed in alcohol and stained by Nissl's method. The cells contain large pigment collections of the usual peripheral unifocal character. The cells of Clarke's column fail to show acute changes. Benda's neuroglia stain demonstrates a large number of corpora amylacea. The Weigert method for myelin sheaths and the Marchi method for fatty degeneration were used in numerous segments of the spinal cord. The dorsal columns of the cervical and, more markedly, of the thoracic portion of the cord show by Weigert's method a central faintly paler area of an oval shape symmetrically set along both sides of the dorsal septum. The Marchi method fails to show especial signs of degeneration in this area. Correlation of the Weigert findings with the data yielded by Mallory's phosphotungstic hematein method leads to the hypothesis that these paler areas are more probably due to an unusual strengthening of the perivascular neuroglia. There is perhaps a localized sheath and fiber degeneration corresponding therewith; but this cannot be demonstrated.

A similar hypothesis can be upheld for the character of the peripheral sclerosis so characteristically shown in phosphotungstic hematein preparations of the spinal cord, particularly in the lateral columns of the lumbar region. Neither Weigert nor Marchi preparations by themselves would with any certainty demonstrate this lesion of the subpial neuroglia.

An occasional ventral root bundle is completely paled out by the Weigert method. The best examples of this were found in the lumbo-sacral cord. The Marchi method in the sections studied failed to demonstrate examples of fresh destruction of isolated bundles, although there is considerable evidence of isolated single fibers impregnated by the Marchi method scattered throughout the cords and the roots.

Cortex Cerebri: In order to work upon a fair sample of cerebral material, sections were prepared from the superior frontal gyri, gyri recti, paracentral lobules, superior temporal gyri, occipital regions, and hippocampal gyri from symmetrical parts of the hemispheres, and stained by Nissl's methylene blue method and by Benda's method for neuroglia after alcohol fixation. These sections were supplemented by sections from hippocampal regions stained in several ways, in particular by Mallory's phosphotungstic acid hematein method, after fixation in Zenker's solution.

Several lesions of a minor character were made out. Of focal lesions may be obtained, first, a relative paucity or in places total absence of Betz cells in the left paracentral lobule, second, a sharply defined lane of destruction to all types of nerve cells cutting radially athwart one portion of the paracentral lobule, so as to efface all layers, in a streak 0.04 cm. wide at first, but flaring out wedgewise opposite the internal layer of large pyramidal cells, to a width of 0.08 cm. (remains of a miliary cortical infarct?)

There are several diffuse or widespread lesions in the cortex cerebri. (1) Pigmentation of the characteristic cells of the fusiform layer of the cortex is exhibited in all regions examined. The pigmentation is found also in the analogue of this layer in the hippocampal regions. (2) Pigmented neuroglia cells are found to some extent in all layers, though to a minor degree in the layers of stellate cells of different regions. There are numerous pigmented neuroglia cells in the middle of the fascia detata. (3) The nerve cell pigmentation, outside the wide spread pigmenting of the fusiform cell layer mentioned above, are a little variable in distribution. The external layer of large pyramidal cells tend to show nerve cell pigmentation more often than the other layers. Nevertheless the internal layer of large pyramidal cells, including the Betz cells, of the right paracentral lobule shows marked nerve cell pigmentation, as also the layer of small pyramidal cells in the right superior temporal gyrus. The occipital gyri, in the samples examined, show little nerve cell pigmentation, although they show considerable neuroglia cell pigmentation.

The nerve cells of the gyri recti and of the occipital regions stain less well than the cells everywhere, showing fewer Nissl bodies and yielding, in the left gyrus rectus, a number of examples of the axonal reaction of Nissl.

The most important lesion found in the hemispheres was a widespread focal superfical gliosis of the fibrillar type, shown in well-nigh every section examined for it. This focal gliosis was well-marked in both hippocampal gyri. In the hippocampal region, moreover, the essential resemblance of these foci to ependymal granules was strikingly brought out On following about the ependyma over the fascia dentata and the subpial region of the hippocampal gyrus, small lenticular glioses are found of approximately the same size and density in the two loci.

The cerebellum was sectioned in numerous places with the object of procuring a fair sample of conditions at large as well as those about the focal lesions.

The cerrebellar tissue at large shows a fair complement of Purkinje cells without notable increase of Bergmann fibers. The granule layer shows a moderate reduction of granule cells with persistence of the eosin structures of Denissenko. The neuroglia framework is delicate but above normal in amount. The increase appears related with a delicate perivascular increase of neuroglia which is best demonstrated in the white matter. The elastic stain demonstrates a general increase of elastic tissue which extends to the smaller vessels, especially well seen in the white core and in the granule layer.

A search was made for focal glioses of subpial distribution, since these might possibly be predicted from the occurrence of such very generally in the spinal cord and in the cortex cerebri. Superficial focal glioses were, however, absent in the parts of the cerebellum examined both by Benda's and by Mallory's method for neuroglia. The absence of corpora amylacea was also noteworthy.

The cystic lesion found at autopsy in the left cerebellar hemisphere resembled in all ways the classical ways of softening. The destruction was massive of all layers and the white core. The cyst liquor with phagocytic cells has in places tremendously dilated the clefts in the adventitia and a much strengthened perivascular neuroglia zone.

The layers differ in their reaction to the destructive lesion and present instructive appearances similar to those described by the writer in 1905.* Even where the fibrillar gliosis in the granular layer appears to be well-nigh maximal, a number of eosin structures of Denissenko persist, as described by the writer in 1906.†

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* "The Neuroglia Framework of the cerebellum in cases of Marginal Sclerosis." E. E. Southard, Journal of Medical Research, XIII, 5, August, 1905, p. 487.

Since the cerebral cortex showed so constantly in numerous examples the characteristic focal superficial fibrillar gliosis, it was thought possible the Weigert and Marchi sections might show evidences in a few places of acute lesions having the same focal superficial character. This was impossible to demonstrate with any certainty. Just as in the spinal cord and spinal nerve roots, so also in Marchi sections of the cortex isolated single fibers were found in various place swhich had been blackened by osmic acid. The regions examined of the present case gave rise to the suspicion that recent lesions could scarcely be excluded from the data in hand.

If, however, we hold ourselves strictly to the data of demonstration, it cannot be denied that these focal lesions may be gradual rather than acute in origin; it can certainly not yet be asserted that these characteristic foci are each one the product of (far less the cause of) an epileptic attack.

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† "Lesions of the Granular Layer of the Human Cerebellum." E. E. Southard. (To be presented.)

Although the cerebral cortex and the spinal cord are thus negative in respect to evidence of immediate nerve fiber injury as demonstrable by the Marchi method, yet it is not infrequent to find by the same method a certain variable amount of phagocytosis in the meninges and in the walls of the small cortical vessels. Clusters of fat-containing phagocytes are found notably in the walls of the small vessels supplying the hippocampal gyri. Perhaps not too much stress should be laid upon the occurrence of such cells in a brain over sixty years of age.

There seems at present no good method of estimating the degree of tissue waste which may be regarded as normal at any age. Moreover, if any importance is to be attached to these fat-containing cells in the cerebral meninges of this case, attention must also be given to the appearance of the same cells in the spinal meninges.

The findings are a bit more positive in Marchi sections of the focal cerebellar lesion, for, in the white centers of a few laminae in the neighborhood of the cyst, bundles of fibers are demonstrable which have been blackened by osmic acid. There bundles of blackened fibers, together with the occurrence of clusters of phagocytic cells containing fat in the walls of the cerebellar cyst, may be taken as evidence of progressive tissue injury in the cerebellar cortex.

REMARKS.

The present case demonstrates how many lesions of different types might be logically assumed to bear some relation to the epilepsy shown in life. It is not easy to pick out the actual relations from the logically possible relations. In the present case of late epilepsy, we may assume (1) that the lesions discovered have no relation with the epilepsy, or (2) that the lesions have a relation but an inessential or adventitious relation to the epilepsy, or (3) that the lesions do play an indispensable part in the epilepsy as (a) antecedents or (b) consequents.

It is doubtless impossible to say which of these assumptions is justifiable. This is equally true, in the total history of work of epileptogenesis, of the relations which have been assumed between epilepsy and various lesions discovered.

The history of work on epileptógenesis reveals a gradual evolution until it is now hazardous to talk of any demonstrable epileptogenic lesions save lesions of cerebral cortex. If epileptogenic agents back of the demonstrable lesions are invoked or epileptogenic agents which produce convulsion and leave no tissue sign are invoked, these agents are usually assumed to work primarily upon the cerebral cortex. Epilepsy has become a problem of cortical physiology, in which the hunt for lesions is incidental and indecisive though fruitful.

Fuller consideration of numerous points in the history of work on epilepsy will show that the disease is more than one of cerebral cortical physiology. Even if we confine ourselves to the nervous system in work on epileptogenesis, we shall find that lesions of very various site may be assured logically enough as related with epilepsy. Work on organic epilepsy is by no means univocal in pointing to the cerebral cortex as the sole epileptogenic zone or as an indispensable epileptogenic *point de passage*. In the literature perhaps the most positive plea for the wider search for epileptogenic centers is the neglected work of Brown-Sequard on epilepsy in guinea pigs subject to lesions of the spinal cord.

I have personally been fortunate enough to secure a number of cases in which it seemed wise not to neglect the cerebellum as in the epileptogenic center. The present case might be offered as such evidence. The strongest point I can make in this direction is that on minute search no other active destructive (in the sense of Marchi-reaction-producing) lesion of a focal character was found in the nervous system except a cyst of softening in the cerebellum. Elsewhere, both in the cerebral cortex and in the bulb and cord, there are found numerous subpial focal fibrillar glioses of a sharp and striking character. These foci of fibrillar glioses were attended by similar sharp and limited irregular foci of glioses along numerous vessels—a kind of miliary disseminated glioses of a perivascular distribution. Moreover, these miliary disseminated glioses of the subpial and perivascular regions were attended by certain granules in the ependyma of the ventricles, which granules were of approximately the same age and character as the miliary glioses. Neither these unusual miliary glioses of the cerebral cortex, nor the more banal neuroglia strengthenings of the spinal cord framework, nor the ependymal granules, were attended by active destruction of nerve tissue (in the sense of Marchi-reaction-producing focal destruction). Yet there was abundant evidence of a diffuse wear and tear in the nervous system in the form of numerous cells phagocytic for fat in many parts of the meninges and perivascular region of the cerebral cortex and spinal cord.

The relation of epilepsy to the cerebellar focus of active progressive destruction is of course in the last analysis doubtful. The relation to epilepsy of the miliary glioses of the cerebral cortex and the focal glia thickenings of spinal cord framework is possibly more doubtful. The characteristic hyperpigmentation of the nerve cells of the fusiform layer may be adventitious.

Investigation of numerous cases of late epilepsy on these lines is indicated.

XIV

A COMPLICATED CASE OF BRAIN TUMOR.

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WITH AN AUTOPSY REPORT

By E. E. SOUTHARD, M. D.,
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The following case is interesting both from the clinical and pathological sides by reason of the varied lesions and post-mortem findings:

The patient, L. W., was a married woman of 45 years and was admitted to the Danvers Insane Hospital on December 12, 1907. The history obtained from the husband is as follows:

Family history unknown. The patient was born in New Hampshire, and, as far as is known, the early life was uneventful. She first married at about twenty years of age and had one child, a boy, who is living and is healthy. She married her present husband 16 years ago. There were no children by this union.

The husband describes her as a mild, even-tempered woman who took things as they came and did not worry over trifles. She attended to her duties as a house-wife in an exemplary manner up to the beginning of the present illness.

The menstrual periods became irregular about four years ago and she passed the menopause about two and one-half years ago. At this time she was nervous and anxious, restless and agitated. After the menses stopped she recovered and regained completely her former disposition.

About twelve years ago she had some womb trouble accompanied with vaginal discharge and pain in the lower abdominal region. This disturbance lasted about three months during which she was unable to do any work but she was not confined to bed. About five years ago she had a left otitis media which yielded to treatment. About two and one-half years ago she again had a discharge from the left ear which lasted several weeks. The discharge occurred for the third time in August, 1907 but lasted only a short time. The husband denies any venereal trouble.

The present illness began in December, 1906. At this time the patient was very nervous, had headaches, and felt anxious concerning herself. The headaches are described as a feeling of a dull heavy pressure and seemed to extend from the forehead to the base of the brain and from which she seemed to gain relief by sleep. Change of position had no effect. She often spoke to her husband of becoming insane and wondered if she would have to go to a hospital. She was irritable and easily fatigued and when she exerted herself became very tired, out of breath and more irritable. She remained in this condition for three or four months and then the husband noticed he had some difficulty in understanding what she said. Her speech became quite indistinct and it would be necessary for her to repeat several times what she wished to say before her husband could understand her. She spoke as if she were tongue-tied. About this time the left side of the body became weak, especially the leg, although the weakness was also apparent in the arm. At times she would seem to give way on the left side. There was also some pain at the base of the brain. About June 1, on the advice of a physician, she moved to the country. After this there was an entire change. She became stupid and drowsy and slept most of the time. She became forgetful and could not remember little things about the house. She would ask her husband about her son sometimes twenty times in an evening without comprehending that she had asked him before. She did nothing on her own initiative but would undertake house-work if told to do it. The quality of the work was below her normal. She was dizzy and fell several times. Since August, 1907, she has taken no interest in anything. She would sit and gaze at space for hours. This continued until November, 1907, when she became quite restless and would sleep only under the influence of a hypnotic. She was untidy in her habits and would wet and soil herself.

About three weeks before admission she began to experience visual hallucinations, she saw pink rats and other animals running about the floor, baby carriages, and, according to her husband, about everything imaginable. For the two weeks preceding admission she had been unable to move about by herself and fell many times. She was very restless and would not stay in any place very long. The day before admission she failed to recognize her husband and asked who he was. At no time was there any nausea, vomiting or convulsive attacks.

On admission physical examination showed a well nourished woman. There was a marked ptosis of the left eyelid. The pupils were contracted, the left being larger than the right, both were central and slightly irregular in outline. It was extremely difficult to determine the light reflexes, but both pupils seemed to contract slightly to direct light and accommodation. There was a marked pyorrhoea. It was impossible to get the patient to protrude her tongue beyond her teeth. The heart sounds were clear and the radial arteries were not palpable.

The left leg was slightly atrophied and the patient was unable to move it. The left arm was somewhat smaller than the right and the patient was unable to flex the forearm on the arm. Muscle strength was less in the left arm than in the right. The left side of the face showed some paresis and the patient was unable to draw her mouth to the left.

The tendon reflexes were slight in the right arm and absent in the left. The knee jerks and patellar reflexes were active on the left side, they were slightly diminished on the right. Babinski's phenomenon was present on the left side, and not on the right. Schaefer's reflex, pressing the tendo Achilles between the thumb and index finger, caused a dorsal flexion of the great toe on the left side, a plantar flexion on the right.

As far as could be determined she could distinguish the head and point of a pin on both upper and lower extremities, on both sides. She was unable to use the left arm, there was no incoordination noticed in the right arm. Stereognosis for coins was good in both hands, the patient answering quickly and correctly.. Several attempts were made to examine the eye grounds but the patient became nauseated and vomited at each attempt.

At no time during her stay in the hospital was there any evidence of hallucinations or illusions. Consciousness seemed to be clouded, the patient was quite apathetic and paid no attention to anything going on about her. Past events of a striking character were retained but there were many lapses. She gave the date as Friday, December 20, 1886, was unable to tell where she was and said she had been here one month. She was unable to answer correctly simple geographical and historical questions. She was able to perform simple problems in addition, but none in division.

The speech defect was quite noticeable. Only by close attention could one distinguish what she said and when asked a question she would repeat it several times before answering. The speech defect seemed to have two components, a stammering due to motor disturbance and an omission of words due to her mental condition. The handwriting showed a marked coarse tremor.

There was some insight, the patient saying that the paralysis followed a shock but she could not realize that the memory was disturbed. There was a tendency to laugh or cry on very slight stimulus.

She remained in bed during her stay in the hospital and gradually became more drowsy and less restless. At times she would weep and attempt to talk but the speech defect increased to such an extent that she could not be understood. About noon on January 22, while her husband was visiting her, she began to have some difficulty in breathing and became somewhat cyanotic. The right eye was turned upwards and inwards and showed a marked nystagmus which did not affect the left eye. The respiration became more difficult and she died at 2.45 p. m.

Autopsy Findings.

The autopsy was performed seven hours after death by Drs. E. T. T. Richards and M. M. Canavan. Following is a summary of such findings as are of interest in the present connection. It is planned to present a fuller account from the histopathological side at a subsequent time.

The cause of death is in doubt. The left middle ear contained 1-2 cc. of greenish pus from which a bacillus of the colon group was recovered in pure culture. The bacillus was not fatal to guinea pigs on intraperitoneal inoculation. The pericardium showed a slight acute fibrinous exudation of recent date. The relation between the otitis media and the pericarditis is in doubt. Culture from the heart's blood was negative, as also from the cerebro-spinal fluid. There was a mild acute degenerative nephritis superimposed upon a chronic interstitial nephritis.

The findings in the nervous system are probably more significant than those of the trunk. Both Gasserian ganglia showed somewhat recent chronic exudative processes of similar character, with giant cell formation and accumulation of lymphoid and plasma cells but without caseation or vascular lesions. Neither tubercle bacilli nor, by the Levaditi method after formalin fixation of one of the ganglia, spirochætæ, were demonstrable in these lesions of the ganglia.

The source and character of the Gasserian lesions are difficult problems. Possibly the left middle ear was the source of an infection with which these lesions are connected. Further work is in progress to find what relation the bacillus of the colon group, isolated from the ear, may have to the lesions. It is probable that the most reasonable hypothesis concerning the lesions is that they are tuberculous, despite the absence of bacilli in the sections. It is probable that the left-sided ptosis may be due to involvement of the third nerve in the chronic exudation, which can be demonstrated to be advancing beyond the capsule of the Gasserian ganglia.

The findings in the central nervous system were manifold:

(1) A dural endothelioma of the left side—the hemiplegic side in this subject—measuring 4 x 3 x 2.5 cm. deep, occupying a position between the superior frontal, anterior ramus of inferior precentral, paramesial frontal, and middle frontal sulci (Quain's nomenclature). Study of the underlying cerebral cortex fails to demonstrate more than a mild gliosis, as a result, doubtless, of the very slow and gradual tissue absorption running *pari passu* with the tumor's development. It was supposed that the tumor might, in some way, be responsible for the homolateral hemiplegia, but further study disposed of this possibility.

(2) Arterio-sclerotic lesions. The basal arteries were smaller than normal and showed areas of sclerosis at points of branching. There was no gross demonstration of arteriosclerosis in the smaller vessels. On section of the pons multiple small cysts of softening containing numerous endothelial cells were found on both sides of the median line. (a) At the level of the isthmus, the most prominent cyst of softening is on the left side, is of crescentric shape, measures 5 x 2 mm., and cuts some of the fibers of the pyramidal tract as well as some commissural fibers. (b)

A second but smaller cyst cuts various pyramidal fibers on the right side at the level of the isthmus, together with many of the deep commissural fibers of the pons. (c) The left brachium pontis is interrupted by an oval cyst, 1 x 0.4 cm., running downwards and outwards almost to the pia-mater. (d) Smaller cysts and vacuolar perivascular spaces occur elsewhere in the pontine region but no particular description of these is made for the present communication.

The case is evidently complex anatomically. The striking dural tumor had actually little to do with the physiology of the patient. The pontine arteriosclerosis must have had much more to do with pyramidal tract interference, although here again there is no massive destruction of either tract. The right-sided tract above the decussation is obviously smaller than the left-sided tract.

An investigation by the Nissl method of the cell pictures of precentral gyri shows that, in the blocks examined, the Betz cells are, with few exceptions, absent on the right side, and present, though reduced in numbers, on the left side. The presence of the tumor on the left side of the cerebrum has effected very little stratigraphic alteration of the underlying cortex. It is not possible to say what is the origin of the disappearance of the Betz cells from the right precentral gyrus. Possible factors seem to be toxic, from the meninges, arteriosclerotic, or secondarily degenerative.

In view of the equivocal character of the various intracranial lesions, including: (1) alterations of the Gasserian ganglia, (2) chronic and subacute meningitis over various parts of the cerebrum, (3) dural tumor of the left frontal region, (4) multiple cysts of softening of the pons, (5) Betz cell atrophy more marked in the right precentral gyrus, it was hoped that the spinal cord findings would clear up the case. The spinal meninges, however, showed an extensive subacute inflammatory process with areas in which the lymphocytes have invaded the cord tissue. The areas of myelitis are chiefly in the periphery and are tolerably extensive in some levels, notable in the thoracic region of the left side. It is quite plain that the meningomyelitis, however recent it may have been, must have modified clinical symptoms through compression of the spinal roots.

The pyramidal tract degenerations in their intraspinal course are about equal on the two sides, so far as can be made out in Weigert preparations. In some levels, by means of neuroglia stains, it can be made out that the left pyramidal tract is traversed by more numerous neuroglia trabeculæ. The diagnosis of more extensive left-sided pyramidal tract lesion in the cord is based rather on neuroglia findings than on myelin sheath findings.

Anatomical Summary.

Acute and Subacute Lesions.

Acute fibrinous pericarditis. Acute degenerative nephritis.
Otitis media (bacillus of B. coli group).
Granulomata, possibly tuberculous, of Gasserian ganglia.
Subacute cerebrospinal leptomeningitis.
Focal encephalitis, by extension from meninges, especially beneath ependyma of posterior cornua of ventricles.
Focal myelitis, especially on the right side in the thoracic region.

Chronic Lesions.

Chronic interstitial nephritis, with atrophy of left kidney.
Slight arteriosclerosis, especially pontine.
Multiple cysts of softening of pons.
Chronic cerebral leptomeningitis.
Betz cell atrophy of precentral gyri, especially right.
Dural endothelioma with lime deposits.
Slight focal cerebral atrophy underlying tumor.
General cerebral atrophy with compensatory oedema of pia mater. Cystic septum lucidum.

Clinical Summary.

It is extremely difficult to ascribe the various symptoms to definite lesions. The pontine lesions are of such a degree that they might easily modify any symptom which could ordinarily be ascribed to the tumor or the meningitis.

A tumor in the frontal region rarely, if ever, gives definite localizing symptoms. In this case the apathy and indifference to her surroundings and also the early headache may be due to it. Its position near Broca's convolution suggests some connection with the speech defect but it is more probable that the lesions in the pons have more to do with it.

The ptosis may be accounted for by the extension from the Gasserian ganglion but it seems very probable that there may have been a nuclear lesion. The visual hallucinations may be accounted for by the meningitis and the dulling of consciousness following it and the tumor.

The lesions in the pyramidal tract explain the Babinski reflex but there hardly seems to be enough difference in the two tract lesions to explain why it should exist on one side and not on the other. There was probably some focal lesion in the cervical cord which interfered with the reflex arc of the left arm and slightly with that of the right which could explain the arm reflexes.

The paralysis of the left side was due directly to the destruction of the Betz cells and this destruction can be accounted for by toxic influences from the meninges or by pressure from the tumor but one would be inclined to give more to the toxic hypothesis.

The case offers nothing new as far as localization is concerned but it does call attention to the vast changes which may be caused by arteriosclerosis and also to the meningeal consequences of a chronic otitis media. In a large number of the cases which have come to autopsy in this institution in the last six months pus has been found in the middle ear. There is no doubt that the middle ear infection has in some cases influenced the clinical picture. The diagnosis of such cases is almost an impossibility as yet but it is worth while to keep such things in view especially as they influence so much the prognosis.

XV

MELANCHOLIA WITH DELUSIONS OF NEGATION: THREE CASES WITH AUTOPSY[1]

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While engaged upon a more general analysis of involution-melancholia, presenile insanity, and allied conditions, our attention was arrested by three cases of melancholia showing feelings of unreality. Recent interest has been so great in patients with feelings of unreality and nihilistic delusions that we have been tempted to anticipate our more general report upon the great subsenile group with a particular account of these three cases. The cases present a certain uniformity both from a clinical point of view and from the histopathological side. Anatomically, the cases belong in the catalogue of insane subjects with "normal" brains or brains with "unimportant" or "trifling" lesions. It is these cases which now deserve the closest histopathological attention, especially from the point of view of the intracellular pigments and fats and their distribution. The problem in these cases of "normal" brains might shift from considering foci of destruction to determining the degrees and loci of intracellular clogging with pigments and fats.

The paper deals with three cases of melancholia which showed feelings of unreality and nihilistic delusions, but is not to be taken as a brief for Cotard's syndrome as an entity among mental diseases. Nevertheless, feelings of unreality and nihilistic delusions, together with various other ideas of a metaphysical cast, are so striking an element in certain conditions of melancholia that we can hardly escape throwing such cases into a group for convenience at least. Moreover, although delusions of this type undeniably dwell in the minds of many persons in and about the climacteric era and although the climacteric state appears to have many features which are met again and again and afford some color to the claim of melancholia as an entity, we do not wish at present to concede that either Cotard's syndrome or melancholia at large is an ultimate group for a finished psychiatry.[2]

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[1] From the wards and laboratory of the Danvers Insane Hospital. The term melancholia is here used in the older Kraepelinian sense.

Histopathology can have little to say on the cerebral side so long as the metabolism of involution presents such meager data. The present cases, however, so far as their examination was carried, offer interesting data which support the claim of a central rather than a peripheral disorder as the basis for the mental states shown. Moreover, the central disorder appears to involve, not so much the great cells which are related to the periphery, as the smaller cells which must be concerned with the elaboration and transforming of peripheral data.

Should our hypothesis hold, the cases of so-called melancholia (including many of those which fall into Cotard's syndrome) might prove to be founded on a central disease. The importance cannot be denied of proving that these patients are not simply explaining and rationalizing their own perverted metabolism, but are actually suffering from a fault in the very mechanism of explanation and rationalizing. Naturally the cerebral fault may itself turn out to be metabolic. We can have nothing to say on this line and offer our cases as preliminary to a more extensive study of the group called melancholia.

Case I.—G. E. H. Admitted to Danvers Insane Hospital July 10, 1903. Age, 49. Occupation, clerk.

Family History.—His father was an eccentric, incapable man, and there was a history of occurrence of insanity in distant relatives on paternal side. The relationship and character of mental disturbance could not be ascertained.

Personal History.—Naturally, he was a man of cheerful, pleasant temperament, with average business capacity. His habits in regard to alcohol were good. There was no history or evidence of syphilis. Previous to present illness he had had lumbago on several occasions, but no well-defined attacks of rheumatism or any other disorder which could account for the cardiac hypertrophy found on admission. The occurrence of previous mental disturbance was denied by relatives. During the winter of 1902–1903, he lost money, became depressed, slept poorly, lost weight and had to give up work in February, 1903. His depression deepened and he became restless and agitated, fancied that he was ruined and in a hopeless condition.

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[2] Since this paper was first presented, Dreyfus has published "Die Melancholie ein Zustandsbild des manisch-depressiven Irreseins," 1907, representing a reversal of Kraepelinian opinions concerning melancholia as an entity.

He was admitted to the McLean Hospital, April 28, 1903. We are indebted to Dr. Tuttle for clinical notes which have been used in the case description. Upon admission at Danvers examination was made by Dr. H. M. Swift.

Physical Condition.—July 11, 1903. His muscular development was good, but he was poorly nourished. Area of cardiac dullness was enlarged to the left, and apex beat was in sixth space. There was a systolic murmur heard most plainly at the apex and transmitted to the axilla. Pulse was 90–100, increased tension, and radials were somewhat thickened. Urinary examination was negative. Cranial nerves were normal. Pupils equal and reacted to light. Tendon reflexes were lively and equal. No disturbance of sensation was found.

The notes on the mental condition from April 28 to July, 1903, are as follows: During the month of May there were short periods when orientation for time and place was imperfect, and at these times he had imperfect memory and displayed great agitation. He was distinctly apprehensive, thinking the register was a machine to kill him; that he had signed away the whole United States; that he had opened all the asylums in the United States; that he had killed his wife and could see her blood on his hands. At times, he appreciated the absurdity of these ideas and would converse clearly. Gradually his apprehensiveness and agitation increased, though at intervals he would demonstrate a good grasp upon surroundings. He became resistive, talked in anxious whispered tones between moans and sighs, and developed the feeling of unreality, seated, rocking body to and fro, wringing his hands; he would whisper between his groans and sighs: "I am all mixed up. It's all a mistake. I'm not Mr. H——. I am all gone, I am dead to the world." Again he would say: "I'm not G. E. H., I ought to be him, but I've taken these names along when I have seen them in the yard. I've made myself as Gibbs, I've been here as G. E. H., and have a home in Haverhill; not I, but G. E. H., has a home in Haverhill. I've made myself a different one."

His agitation increased, and he became untidy and very resistive. His productions became desultory and disconnected. He denied identity, had no stomach, could not take food, and at the last had no idea of time or place. He died of pneumonia July 13, 1903.

Summary of Case I.—Father was eccentric and there were instances of insanity on paternal side of family. Age, 49. Habits exemplary. Loss of money only recognizable cause for gradually increasing worry and depression. No serious illness previously. Cardiac hypertrophy, arterio-sclerosis, only recognized physical ailments.

Mental symptoms appeared in following order: worry, insomnia, restlessness, depression, delusions, possibly visual hallucinations, agitation, ideas of negation and stuporous condition preceding death. Orientation fairly well preserved until the last few days.

Autopsy Findings.—The autopsy was performed by Dr. A. M. Barrett and showed death due to pneumonia of the right lower lobe, lower portion of upper lobe, and posterior portion of the middle lobe of left lung. The heart muscle was pale and flabby. The mitral valve was moderately thickened. There were a few patches of atheroma in thoracic portion of the aorta. The liver showed slight surplus of fat. The heart weighed 445 grams. There was a chronic fibrous peritonitis in the region of the appendix and upon the lower surface of the liver and around the gall-bladder. Examination of the skull showed the sutures preserved and the diploë in large amount. The dura mater firmly adherent to the calvarium. The brain with pia mater weighed 1445 grams. The pia mater contained considerable fluid and was hazy along the edge of vessels. Adhesions were found at the bottom of the fissures of Sylvius. The large blood vessels at the base showed some yellow atheromatous patches of irregular distribution. The lumina of the arteries were not diminished. The choroid plexuses showed a few minute cysts. There were no focal areas of softening in the brain. The ependyma of the ventricles was smooth.

Microscopical Examination.—Several regions of the cerebral cortex in both hemispheres showed an essentially normal layering (Nissl's method). There are nowhere focal destructive lesions. One lesion is common to all the sections examined, viz., a great quantity of pigmented cells in the adventitiæ of the vessels in all parts of the gray and white matter (best demonstrated in Heidenhain iron hematoxylin preparations). The pigment around the larger vessels is enclosed in cells of the usual meningeal phagocyte type. But about the capillaries of the gray matter the pigment is as a rule enclosed in neuroglia cells.

The source of the perivascular pigmentation cannot be made out from the vessels affected, since all the vessels with but few exceptions are equally invested with pigmented cells. The distribution of pigment in neuroglia cells is a little more characteristic. The pigmentation of neuroglia cells is not, as in some conditions, particularly found in the outer or subpial layer or in the inner or fusiform cell layer. The neuroglia cell pigmentation tends to affect the intermediate layers of the cortex. This is best shown in the layers of large and small stellate cells of the calcarine areas. The frontal areas, however, show a fairly general distribution of pigmented neuroglia cells.

The nerve cell pigmentations are more characteristic in point of distribution. The large pyramidal cells of the frontal cortex are practically all pigmented and, in most cases, somewhat characteristically along the lateral borders and at the inferior angles, leaving the perinuclear region and the apical portion free of pigment. The pigment is not collected in a single sac, but appears to occupy interstices of the cells with perfect maintenance of their proper contours. The characteristic unifocal collections of pigment in the Betz cells of the paracentral lobules are absent in this case. The Betz cells have little or no pigment of any sort. The larger nerve cells (including the solitary cells of Meynert) of the calcarine areas fail to show much pigment.

The examination indicates a steady outward stream of pigment materials from the nerve tissues to the perivascular region. So far as the examination of a limited number of areas is conclusive, the autochthonous pigmentation of the nerve cells is maximal in cell types whose function is either unknown or receptive. Large elements like the Betz cells and the solitary cells of Meynert fail to show marked pigmentation. These larger elements are doubtless more directly related with the projection system than the others.

Case II.—T. H. Admitted to Danvers Insane Hospital June 13, 1904. Age, 75. Occupation, mason.

Family History.—Both maternal and paternal relatives were unusually healthy, long-lived people. His mother died at the age of 63, and had exhibited a continuous, melancholy depression for the last few years of life. One brother died of apoplexy at the age of 52. Family history was otherwise negative.

Personal History.—He had a normal development and became a capable and modestly successful contractor, retiring from business at the age of 65, with a small competency. His temperament was cheerful and sociable. Family relations were pleasant. At no period of life had he ever used distilled liquors, but occasionally he drank a little beer with meals.

At the age of 25, he had a venereal lesion, probably nonspecific. Aside from an attack of pneumonia seven years prior to commitment, he had always been healthy. His relatives had noted some memory failure for recent events during a few years before admission, and he had been troubled with insomnia for one year, but no symptoms of insanity were recognized until the week before his commitment. The loss of an only son eight years before, who left a widow and four children dependent upon the patient for support, had been the only known cause for worry. A sudden depression developed. He thought he had lost all his property and that he was responsible for the consequent misery of his family. He became sleepless for a week and finally cut his throat, wounding the larynx. He struggled to prevent dressing of the wound, declaring that he did not want attention, that he must die; and threatened to accomplish suicide by some other means. He was soon admitted to the hospital.

Physical Condition.—He had a powerful muscular development, was well nourished, tissues showing very little senile atrophy. There was an infected wound involving larynx. Temperature on admission 99.4°. There was harsh respiration and occasional coarse rales were heard over anterior surface of chest. Area of cardiac dulness slightly enlarged. Second aortic sound was sharp and accented. First sound at apex was roughened. Pulse was 126, fair tension, irregular rhythm and occasionally intermittent. Superficial arteries were thickened and tortuous, and there was well-defined arcus sensilis. Urine showed trace of albumin. No sugar. Sediment contained hyaline casts, pus cells, uric acid and calcium oxalate crystals. Strength was little impaired and he had perfect control of muscular movements.

Cranial nerves were normal. Pupils were responsive to light. Tendon and skin reflexes were normal. No sensory disturbance detected.

Mental Condition.—At time of admission, he was oriented for time, place and persons, and appreciated the character of his surroundings, but answers had to be obtained between his groans and protestations. His mental distress and agitation rapidly became more pronounced, and he would pace about his room, wringing his hands, his features contorted with emotion, muttering about his "most miserable state," his family and his deplorable acts. With great and steadily increasing difficulty his attention could be gained momentarily, but most of the time he took little notice of requests and struggled blindly against efforts to care for him. His spontaneous talk showed great depression, nihilistic delusions with the feeling of unreality; *e. g.*, "Oh! I am in a hopeless state. It is awful and nobody ever suffered this way. This is not a reality. This is eternity, this is eternity. Why such a thing as I the world never knew, the world never saw. Why! Why! Why! I can't move, I can't die." As nourishment was offered he said: "No, no, I can't take it. It won't do me any good. I can't take it, I am not a reality." At another time, he declared he was in a vault, and that the sunlight, streaming into the room was not real; that the sky was not blue; that the view from his window was not a reality; that the people about him were not real human beings, and that no person had ever been in such a miserable state as himself. His agitation was practically continuous. He would appear exhausted and lie down and secure short, fitful sleep. The suppurating laryngeal wound eventually, prevented audible speech, and death resulted from pneumonia on the eighth day in hospital.

Summary of Case II.—Mother had mental depression during last four years of life. Brother apoplectic. Age, 75. Moderate beer drinker. Old age and worry over loss of son and responsibility of caring for son's family only known causes for a comparatively sudden outbreak. No known illness, excepting pneumonia, seven years previously. Arteriosclerosis, nephritis, myocarditis and bronchitis from wound in larynx were the only physical ailments noted. Slight memory failure and some insomnia preceded for some months a sudden depression, painful delusions concerning self and family, suicidal attempt, great motor agitation, feelings of unreality largely confined to external objects, and nihilistic ideas. Orientation fairly preserved to the last few days of life.

Autopsy Findings.—The autopsy was performed by Dr. A. M. Barrett and showed death probably due to hypostatic pneumonia. Suicidal wound of neck. The heart was fatty. Arteriosclerosis was general, involving the aorta and in particular the splenic vessels and the arteries of the base of the brain. There was well-marked chronic diffuse nephritis. Examination of the head showed the following: dura mater completely and firmly adherent to the calvarium. The pia mater free from thickening. Basal arteries beset with scattered foci of yellow thickening. Internal carotid arteries notably stiff and yellow. Small old cyst of softening just outside tip of posterior horn of right lateral ventricle. The brain with pia mater weighed 1,300 grams.

Microscopical Examination.—The frontal, paracentral and calcarine regions of the cerebral cortex show essentially normal layering. The most prominent feature is a universal pigmentation of perivascular cells, neuroglia cells, and nerve cells of about the same degree in all regions examined. The pigmentation about the vessels is by no means maximal, and is of a degree often shown in younger subjects under different conditions. The neuroglia cell pigmentation affects practically all the cells and, since it occurs also in the subpial layer, is probably due to fiber degeneration as well as to nerve cell changes. Satellite cell pigmentation is, however, also frequent and characteristic, so that a nerve cell origin for some of the pigment is highly probable. The examination of the nerve cell pigmentation is facilitated by parallel study of adjacent sections stained by Nissl's methylene blue method and by Heidenhain's iron hematoxylin method. By Nissl's method it is easy to make out the universality and extent of the senile yellow pigmentation in the layer elments, *e. g.*, large pyramidal cells, Betz cells, solitary cells of Meynert. Besides the yellow pigmentation of the banal type shown in old age, the Heidenhain preparations show an extensive development of pigment staining black by this method. This latter black-stained pigment lodges in the nerve cells of the intermediate layers, but characteristically affects the smaller elements, *e. g.*, small pyramidal cells, as well as also the large pyramidal cells (in which the black-stained pigment accompanies the yellow pigment which remains unstained). The Betz cells and the solitary cells of Meynert, despite their accumulations of or distention with yellow pigment, fail to show more than a very few black globules in the Heidenhain preparations. The black-staining pigment seems never to alter the cell form, but to lie in crevices which may represent lost tissue. The Nissl stain shows that the Nissl bodies are throughout not well stainable; but this circumstance cannot yet be unequivocally related to the cell pigmentation.

The arteriosclerotic element in this case is not prominent, despite the old cyst of softening in the left occipital region. Nor is cerebral atrophy a prominent feature. The most striking features are extensive pigmentations, which are partly of senile origin and partly reside in elements which are of unknown or receptive function. These two types of pigmentation are easily separable in the Heidenhain preparations.

Case III.—J. H. A. Admitted to Danvers Insane Hospital, November 21, 1903. Age, 65. Occupation, shoemaker.

Family History.—Patient's father died of some cardiac disorder at age of 77. His mother died at the age of 67, after suffering from senile dementia for over three years. One brother died of tuberculosis. The history concerning grandparents and collateral branches was unobtainable.

Personal History.—Nothing was known of early life. He enlisted in the army, serving three years during the Civil War, and was afterwards employed as a shoe-factory operative. He was married in 1873, and has two healthy adult children. His wife stated that he had been industrious, kind to family, pleasant and agreeable in disposition. Since early life he had been a moderate user of tobacco and alcohol. He was not a daily drinker and was never known to have been intoxicated.

He had had a purulent discharge from the right ear following scarlet fever at the age of three. This was the only severe illness he had had until the age of 61, when he had typhoid fever and la grippe during the same year and was mildly delirious during both illnesses. He made good recoveries and worked steadily until nine weeks before his commitment, when he was discharged for failure to perform work properly. For two or three months previous to this event he had slept poorly, lost weight, worried over trifles, and had shown evidences of mild hypochondriacal depression. Following the loss of his position, mental symptoms had been progressive. He began to think that he and his family would starve and freeze, and was greatly distressed by fancied physical ailments; *e. g.*, he had the idea at one time that his head, eyes and limbs were growing large and later thought that he had become much smaller than others who were correspondingly increased in size. Occasionally he would seem to have some insight, and he lost weight steadily. He never showed any suicidal tendencies. A sudden threat of violence to members of his family and refusal of food were the immediate causes of his hospital commitment.

Physical Condition.—He had slender muscular development, pallid complexion and was poorly nourished. His skin was dry and wrinkled. He had sordes on lips and teeth, tongue was coated and breath foul. Temperature ranged from 99° to 100°. Area of cardiac dulness was not increased. Second aortic sound was sharp and accented, and first sound at apex was roughened. Pulse was 96, feeble volume and irregular rhythm. Arteries were soft. There was a faint arcus senilis.

Abdomen was shrunken. Urine was turbid and had a foul odor. Acid. Sp. gr. 1013. No sugar or albumin present. Sediment showed squamous epithelial cells, few red corpuscles, bacteria and moulds. He had accurate control of muscular movements, and walked with a firm gait. He could hear faint watch tick with left ear and could read coarse print. The right pupil was slightly larger than left, and both reacted promptly to light. Tendon reflexes were generally hyperactive and equal. Sensory tests were of little value, as he declared that he had no feeling, although wincing at pin pricks.

Mental Condition.—Soon after admission, he objected to every effort to care for him. He refused to walk, said that he had no legs and could not stand; when an attempt was made to raise him from a sitting position he doubled up his limbs and shouted protests against the cruelty of trying to make a man with no legs walk. His enunciation was not impaired and he talked freely, excepting that he would refuse to answer some questions and remain mute for a short time. In answering questions to test orientation, grasp on surroundings and retention of school knowledge, he would give correct replies after protests, refusals, and nihilistic statements; *e. g.*, Q. Where are you? A. "I don't know, I've got no brains. Yes I do too, Danvers. I've been here. Down here for insane and you are going to report I am all right." Q. Are you sick? A. "Course I am, and you know it. I've got no brains and I can't talk and you are going to make out the wrong report. I've got no heart and no stomach, and I can't swallow. I haven't any feelings." His tones were sharp and manner petulant. He was apprehensive and showed some agitation. There was no evidence of retardation. After much urging he would swallow liquid nourishment in great quantities, but saying it did him no good, because he had no stomach, nothing but a hole and he would drink to fill that up. Every question would suggest some new idea. When asked if he knew any people about him, he answered: "Yes, you are all great big men and so strong, you must weigh over 400 pounds, and I'm so small you can't see me. I'm freezing to death and you cover me up with great, heavy, wet blankets. I wouldn't burn if you threw me in the hottest furnace, but I can't suffer because I've got no brains."

He would say that he could remember nothing of events from day to day because he had "no brains" and in the same sentence make remarks that showed partial recollection. Depression was constant and at times was very marked. During the first week in hospital he was restless, walking to and fro in his room, groaning and picking at his clothing and fumbling with his bedding. He was occasionally untidy in habits. With increasing weakness, his ideas of negation and unreality became more absurd, and were more brokenly expressed. Death occurred December 19, 1903.

Summary of Case III.—Mother died of senile dementia at 67. Moderate use of alcohol. Age, 65. No assignable cause for insanity. Typhoid and la grippe with delirium accompanying both disorders, four years previously.

Emaciation, arteriosclerosis of mild degree, nephritis, cystitis and lively reflexes were the only important physical ailments. Mental symptoms gradual in onset. Slowly increasing hypochondriacal depression, with incapacity for work, was noted for four months before evolution of ideas of unreality and nihilistic delusions. Mildly agitated, petulant and complaining during the last. Orientation and memory quite well preserved.

Autopsy Findings.—The autopsy was performed by Dr. A. M. Barrett, and showed an extensive suppurative process in the retroperitoneal tissue around the bladder with abscesses anterior to the bladder and numerous narrow sinuous pus channels running backward on either side of the bladder. The process extended upward beyond the limits of the pelvis into the perinephritic fat tissue as far as the upper poles of the kidney.

The right auricle of the heart showed numerous small thrombi. There were numerous recent emboli in the primary branches of the left pulmonary artery. The aorta showed, 30 cm. below the arch, a large thrombus with puriform softening. The spleen had failed to react to septicemia. The lungs, pancreas, renal pelves, ureters and bladder showed various signs of acute inflammation. Moderate aortic sclerosis. The brain showed no gross signs of alteration at the autopsy and was hardened for four weeks in ten per cent. formaldehyde solution. More careful examination later also proved negative. The ependyma of ventricles was smooth.

Microscopical Examination.—Cultures from the heart's blood and retroperitoneal pus showed pneumococcus and a bacillus, probably bacillus coli communis. Examination of the organs of the trunk added little to the gross findings. The kidneys showed a mild chronic interstitial change with slight fatty changes in the epithelial lining of the tubules.

Microscopical examination of the various regions of the cerebral cortex by Nissl's method, by L. Ehrlich's pyronin method for plasma cells, and by Heidenhain's iron hematoxylin method demonstrated a moderate and in places quite trivial accumulation of cells of the lymphocyte group in the sheaths of small vessels in the lower layers of the gray matter and the adjacent white matter. This accumulation of lymphocytes (and plasma cells) is strikingly even in degree in the parts examined (left and right superior frontal, left and right paracentral, left and right calcarine and occipital regions) and in most sections has to be sought with some care. There is no noteworthy alteration of the nerve-cells, if we except pigmentation of the larger elements (large pyramidal cells of frontal area, Betz cells, large pyramidal cells of occipital area). The other nerve elements (in particular the solitary cells of Meynert) fail to show pigmentation. Numerous neuroglia cells, as well as cells applied to the walls of capillaries, are well pigmented (seen especially in the Heidenhain preparations). The cell layers of the cortex and the cell arrangements of the white matter show no notable alteration.

The question arises whether the data admit the diagnosis *general paresis.* A strict histological diagnosis might be chronic degenerative and exudative encephalitis of a diffuse but mild nature with the exudative element slightly predominant.

SUMMARY OF POST-MORTEM FINDINGS.

The causes of death were: Case I, pneumonia; Case II, pneumonia following suicidal wound of neck; Case III, general infection from pelvic suppuration.

All three cases presented more or less sclerosis of the aorta. The senile case (II) and case I showed considerable sclerosis of the large arteries of the base of the brain.

Aside from a small old cyst of softening in case II, no brain showed focal destructive lesions. No brain gave sign of general or focal atrophy upon macroscopic examination. Case I was the only case to show pia mater changes, and these were confined to haziness along vessels and adhesions at the bottoms of the Sylvian fissures. Case III, despite the chronic exudate found upon microscopic examination, showed no macroscopic alterations of the pia mater. The ependyma was in all cases smooth.

Microscopical examination of three or more areas in each hemisphere was carried out by several methods, notably by Nissl's original methylene blue method and by Heidenhain's iron hematoxylin method.

Common to all the cases is an accumulation of meningeal *phagocytes containing pigment.* This perivascular pigmentation is of about the same degree and quality as that found in most adults beyond the age of fifty years. Whether perivascular cell pigmentation signifies increased wear and tear on the part of the nervous tissues, or whether it rather signifies a reduction in the serum's power to take up these substances cannot yet be told with assurance.

A second common feature of the cases is *neuroglia cell pigmentation.* Whether the collections of pigment (or of fat-like bodies) here shown indicate phagocytosis on the part of these cells cannot be established. The accumulations of fat-like substances might be due to some neuroglia cell activity affecting materials brought to the cells in solution. The senile case showed well-marked satellite-cell pigmentation. The neuroglia-cell pigmentation which is found common to all three cases is pigmentation of the scattered neuroglia cells of the middle layers of the cortex.

The nerve cells also show deposits of pigment or fat-like substances. The Heidenhain preparations bring out the presence of two kinds of pigment, which can be distinguished according to capacity or lack of capacity to take up the hematoxylin. The type of pigment which fails to take up hematoxylin is collected in the familiar yellow sacks which form unifocal deposits in the cytoplasm of the larger cells. This yellow pigmentation is found in case II, as it is in numerous senile and subsenile conditions. It is this pigment which is so common that histologists attach little significance thereto. The other kind of pigmentation, so well demonstrable by the Heidenhain method, is developed in all of our three cases. It is in this pigmentation, if in any feature now demonstrable, that we must look for somewhat differential characters in diseases of the group under discussion. The most significant feature of this type of pigmentation is its plurifocal distribution in the affected cells. Whereas the yellow sacks of the more banal type of pigmentation seem to enter into no intimate relation with the cell and may not interrupt its paths, the plurifocal pigmentation, on the contrary, is so distributed that it may well modify or influence the progress of impulses through the cells. It may be noted that this kind of pigment is apt to be deposited at the sides and inferior angles of the cells (*e. g.*, of the large pyramidal cells of the frontal cortex) and to neglect the perinuclear and apical portions of the cells.

If we take into account the iron-hematoxylin-staining pigment and leave out of account the banal yellow pigment, it appears that the larger elements (*e. g.*, Betz cells, solitary cells of Meynert) are not likely to be affected. The iron-hematoxylin-staining pigmentation proves to be maximal rather in those elements whose function we do not understand or term receptive. If this pigmentation can be taken as a sign of central disease, the disease appears to involve not so much the larger elements which come into immediate relation with the projection system as the smaller elements having to do with transference of impulses or having unknown functions.

General Summary and Remarks.

The disease group melancholia has a somewhat precarious footing in present-day psychiatry. The purest cases appear to occur in or about the climacteric era. The practical alienist is always reluctant to place a case in the group melancholia, lest it shortly transpire that the case should rather have been counted senile, or arteriosclerotic, or, in some other way, frankly organic. Moreover, it frequently appears that error may creep in the opposite direction and the patient, alleged to have melancholia, turn out to be actually a victim of some constitutional defect or of some acute psychosis.

We have found difficulty in resolving our ideas about the disease group melancholia and were for a time inclined to believe that any given case could perhaps be transmuted, as a matter of diagnosis, into some other group.

As a beginning in this group, we have here introduced three cases which, whether they fit any acknowledged grouping or not, appear to have certain features in common as well as certain instructive differences. The psychological color and, to some extent, the course of these cases recall some features of Cotard's syndrome.

In every case there were a few established instances of insanity in the direct line on one or other side. The hereditary features, interesting in each case, appear to have little in common, except the terminal continuous depressions in the mothers of two patients (cases II and III).

The lives of the three patients showed little which can be regarded as underlying their ultimate conditions. Case I used no alcohol, Case II drank beer with meals, Case III used alcohol moderately. Venereal history practically negative in all cases.

Occupations: clerk, I; mason, II; shoemaker, III.

Previous diseases: lumbago, I; pneumonia seven years before commitment, II; scarlet fever and purulent otitis media, æt. 3, and typhoid fever and la grippe with delirium, æt. 61, III.

Ages at onset: 48, I; (69) 75, II; 65, III.

Durations: 8 months, I; (8 years) 2 weeks, II; 24 ca. weeks, III.

Onset: gradual, I, III; sudden, II.

Assignable causes: financial worry, I; senility and domestic worry; nothing, æt. 65, III.

Physical conditions: arteriosclerosis in all cases; case III showed emaciation, nephritis, cystitis, increase of reflexes.

Mental states: ideas of negation in all cases, developing in case I after slowly increasing depression and agitation with delusions about self and family and questionable hallucinations; in case II, after gradual senile failure, as sudden deep depression with agitation, delusions of ruin of self and family, and suicidal attempt; and in case III, after slowly developing hypochondriacal depression.

The feelings of unreality and ideas of negation presented a certain variety in the three cases. Case I showed an alteration of personality, uttered frequently in such phrases as "I'm all gone, I'm dead to the world. I'm not G. E. H. I've made myself as Gibbs; I've been here as G. E. H." Case II showed a feeling of unreality, both as regards the outer world ("sunlight not real, sky not blue, people not real human beings") and as regards himself ("I can't move; I can't die"). Case III showed an alteration of point of view as to the outer world ("you're all great big men, and so strong; you must weigh over 400 pounds") and nihilistic ideas ("I am so small you can't see me; I've got no brains; and I can't talk; I've got no heart, and no stomach, and I can't swallow; I wouldn't burn if you throw me in the burning furnace").

The anatomical side of these cases presents several common aspects, but little which promises to explain the disease. Arteriosclerosis, when confined to the large branches of the circle of Willis, can scarcely be invoked as underlying symptoms of such specialized character as those under consideration.

Just as the patients showed strikingly little in alterations of reflexes (increase in case III), so the brains showed strikingly little in the shape of gross or focal alterations (small old cyst of softening in case II and mild chronic exudative process in case III).

Moreover, the brains gave little evidence of general or focal atrophy. No striking alterations in cortical topography and arrangement of layers could be detected on microscopic examination. Pigment-bearing cells in perivascular spaces were constantly found; and, in default of any suspicious localization of these, we must attribute them rather to the results of advancing years than to a special factor.

Neuroglia cell pigmentation was also quite constantly found; but this was not so universal in distribution as was the case with the perivascular cell pigmentation. Common to all three cases was a neuroglia cell pigmentation in the intermediate layers of the areas of cortex examined. The relation of the neuroglia cell pigmentation to cortical activity could not be made out. Satellite-cell pigmentation was not constant.

Nerve cell pigmentation was constantly found in the elements of moderate size in all parts of the cortex examined. This pigmentation was strikingly brought out by the use of iron hematoxylin. The pigmentation in question has a somewhat characteristic locus in the affected cells, fails to destroy their contours, and lies apparently in interstices in the cells. This interstitial nerve cell pigmentation, as brought out by iron hematoxylin, is to be sharply distinguished from the familiar yellow sack pigmentation of the major elements.

Pending the increase of knowledge concerning the pigments and fat-like deposits in general, we can at least investigate their occurrence topographically. It seems to us that, however fragmentary the present findings are and however far we may be from bringing such findings into relation with disorders of apperception, we have at least a promising field for investigating the conditions of what seems to be a truly cortical disorder. We are at present at work upon accessible cases of melancholia.

XVI

FURTHER STUDIES IN ANAPHYLAXIS.*

I. *On the Mechanism of Serum Anaphylaxis and Intoxication in the Guinea-pig.*

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The hypothesis which we offered a year ago[1] as explanatory of the mechanism of the anaphylaxis in guinea-pigs, which follows an initial injection of horse serum, and of the intoxication which evidences this increased susceptibility, occurring on a second injection of the same serum, differs essentially from the explanations of other workers on this subject. While we in no manner wish to assert that the working hypothesis which we have employed does more than approximate the ultimate truth of this interesting condition or reaction of the animal body, our further study not only has convinced us that our explanation best agrees with the acquired facts, but that the opinion held by the majority of those who have attentively considered the problems of anaphylaxis is no longer tenable. The commonly accepted hypothesis is that increased susceptibility is due to the presence of some form of "antibodies," and that intoxication subsequent to anaphylaxis is due essentially to the participation of "antibodies" in forming some toxic substance with the antigen.

It will be necessary to consider as briefly as possible certain of the essential facts that are known concerning anaphylaxis in general, and more especially the anaphylaxis shown by guinea-pigs to horse serum.

Although the reaction of tuberculous animals to the injection

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of tuberculin has been known and utilized for diagnosis for a number of years, the proper appreciation of its meaning as an instance of anaphylaxis and of its correlation with similar important though less obvious reactions in animals, was not fully brought out until recently by the work of v. Pirquet, Calmette and others on tuberculosis and on such diseases as small-pox. There is no doubt that a condition of immunity frequently occurs in association with increased susceptibility, but these two conditions of diametrically opposed import to the organism have not been proved to be in any way interdependent. That anaphylaxis is simply a "stage in the development of immunity" is an opinion recently expressed by so high an authority as Richet[2]; but whether this be true, or anaphylaxis be due to a reaction in the body of a nature distinct from the reactions of immunity, as we suspect, the recent studies have at least opened an interesting field of obvious value to our knowledge of the struggle of the organism with disease.

To Otto,[3] and to Rosenau and Anderson[4] working independently, we owe the impetus which has been given to the study of anaphylaxis by the concrete instance which they have demonstrated of the increased susceptibility of guinea-pigs to horse serum, evidenced by the intoxication of these animals on a second administration of serum. These writers found that although normal guinea-pigs support, without symptoms, the injection of any convenient amount of horse serum into the peritoneum, guinea-pigs that have previously been used to test the potency of diphtheria antitoxin (horse serum) or had received a tiny dose of normal horse serum without the addition of the diphtheria toxin present in the toxin-antitoxin mixture would, on a subsequent injection of a relatively large amount of horse serum (five cubic centimeters) into the peritoneum, show severe symptoms of intoxication and frequently die. This reaction of intoxication is, as far as observations extend, present at practically any period of the animal's life subsequent to a necessary period of incubation of about ten days, following the initial dose of serum. It was further shown that animals which had received a large initial dose (four to five cubic centimeters) instead of the usual small dose (.002–.01 cubic centimeter) failed to react after the ordinary incubation period (Otto); and Rosenau and Anderson showed that animals which had received several relatively large, spaced injections (one to two cubic centimeters) showed no symptoms, if injected with a large dose of serum after ten days, and had to all appearances become "immune." The blood of such "immune" animals, however, had no effect in neutralizing the toxic property of horse serum when mixed with it and administered to a sensitive pig. Rosenau and Anderson in particular made a careful study of the effect of various conditions on the toxicity of horse serum, and in addition ruled out certain possibilities such as the formation of precipitates which might have been supposed to cause the intoxication. As a result of their experiments both Otto and Rosenau and Anderson came to similar conclusions as regards the nature of the hypersusceptibility caused by the initial injection, and the intoxication following the second injection. They regard the injection of a small amount of serum as giving rise to "antibodies" which unite with the antigen in horse serum on a second injection and produce a combination toxic to the animal; the injection of a large initial dose or several successive doses would give rise to an immunity, the exact nature of which is not stated. Whether the immunity might depend on the presence of a larger amount of antibodies similar to those which cause the intoxication in the first instance, or on the presence of antibodies of a different nature, is uncertain. At any rate the animal was considered "immune" in the sense that it did not react, although its blood had no power of neutralizing the toxic action of horse serum. In other words, the substance in horse serum which gave rise to the "sensitization" and the substance which intoxicated were identical, as indeed would be essential to explain the intoxication according to the Ehrlich scheme of immunity.

There followed observations by Besredka and Steinhardt,[5] who pointed out that if the toxic dose is injected directly into the brain a much smaller dose will kill; these authors, therefore, were inclined to localize the reaction to some lesion of the brain cells caused by the first injection and intensified by some interaction on the second injection.

Gay and Southard,[1] in their studies on serum anaphylaxis, made several novel observations, as the result of which they came to conclusions regarding the mechanism which are essentially different from the " antibody hypothesis " of the earlier observers. It was found in the first place that the intoxication of guinea-pigs when evidenced by severe symptoms, whether or not followed by death, was almost constantly accompanied by macroscopic lesions in the nature of hemorrhages, which occur in practically any organ of the body, heart muscle, lungs, spleen, and the like, but more particularly in the stomach; microscopically, it was found that these lesions were associated with cellular alterations in the nature of fatty changes, and in some instances, as in the stomach, the fatty changes in the endothelium seemed the cause of the hemorrhages. None of these lesions were noted in a number of " normal " and " sensitized " controls. These authors further demonstrated that the so-called " immune " animals, which had received a single large injection or several spaced injections, eventually become quite as susceptible as do animals which have had a small initial dose, the incubation period varying directly with the amount injected on the first dose or doses. It seemed more correct, then, to refer to these animals as " refractory " rather than " immune." It was further noted that the offspring of such refractory animals, born during a period of full refractoriness in the mother, were not themselves refractory, but sensitive to intoxication by horse serum. It was then determined that normal guinea-pigs which were given small amounts (.1 of a cubic centimeter) of serum from either sensitive or refractory guinea-pigs were themselves sensitive if tested at the end of ten days. This transmitted sensitivity was considered purely an active one, and due to the presence of an unneutralized sensitizing element of horse serum for which the name "anaphylactin " was offered, the function of which was stimulation of the cells of the host which led to an overactive assimilation of, and intoxication by, those other elements of horse serum which had been eliminated in the case of "sensitized" guinea-pigs. The state of refractoriness would be due, then, to the incomplete elimination of the assimilable substances. This conception would assume the existence of two separate substances in horse serum, a sensitizing substance (anaphylactin) which is not assimilable by the guinea-pig tissues, and therefore not easily eliminable, and toxic substances which are assimilated by the guinea-pig tissues. In order to prove that there are these distinct substances in horse serum, recourse was had to injections of "refractory pig" serum directly into the circulation of sensitized guinea-pigs; it was found that although .005 of a cubic centimeter of horse serum injected into the carotid of a sensitive pig will produce symptoms, and .02 of a cubic centimeter will kill; that 1.5 cubic centimeters of refractory pig's serum, which will sensitize normal guinea-pigs in the dose of .1 of a cubic centimeter, produced no toxic symptoms in highly sensitive animals. As the intoxication of sensitive guinea-pigs is evidenced by acute cell lesions in various parts of the body, and the rapidity in the evolution depends on the intimacy and rapidity with which the horse serum comes in contact with the cells, the writers attempted to ascertain whether the intoxication is due to a toxic substance found in the blood stream of the sensitive guinea-pig and then reacting on the cells, or due to a direct action of horse serum on cells "prepared" by the anaphylactin. It was found that mixtures of sensitive guinea-pig serum plus horse serum produced no effect on normal guinea-pigs when injected directly into the circulation, as indeed had been noted by Rosenau and Anderson, and the conclusion was properly drawn that in all probability the reaction of intoxication is located within the body cells, and evidenced, as has been stated, by a rapid fatty change.

It is evident that in this, the most fruitfully studied instance of anaphylaxis, the anaphylaxis of guinea-pigs to horse serum, we have two definite explanatory hypotheses concerning the mechanism of the hypersusceptible condition and its demonstrative intoxication; the hypothesis of Otto, and of Rosenau and Anderson, which may be called the "antibody" hypothesis, and the anaphylactin hypothesis of Gay and Southard, which asserts the existence of two separate components in the active serum, one of which intoxicates and one of which sensitizes. It must be admitted at once that the antibody hypothesis has had practically the united adherence of the workers * on other undoubtedly analogous instances of anaphylaxis, whose opinions, however, are founded mainly on clinical evidence, and in no instance on so well studied an instance of hypersusceptibility as is this serum disease of guinea-pigs.

Since our last publication we have persistently directed our attention toward a further understanding of this horse serum anaphylaxis in guinea-pigs, rather than toward the accumulation of correlative evidence from other forms of hypersusceptibility, and our opinions on these other instances are based largely on literary evidence; our effort has been to gain evidence rather by simplifying known conditions, than by multiplying instances. And in this connection we should like to insist on one point of difference between our work and that of some other observers; with a single exception, which was carefully noted in our first paper, our interpretations have been founded on the intoxication of guinea-pigs sensitized with a uniform anount of *normal horse serum*, and not on animals sensitized with a toxin-antitoxin mixture. It is admitted by Otto[6] and by Lewis,[7] who have both made use, apparently indiscriminately, of animals either sensitized by horse serum alone or by a toxin-antitoxin mixture, that the toxin-antitoxin mixture renders the animal more sensitive than serum alone. While the employment of "used" toxin-antitoxin pigs has the advantage of economy and may, indeed, lead to no erroneous interpretation of results, it is scarcely to be advocated as a clean experimental procedure.

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* No especial reference is here made to those authors whose theories of anaphylaxis agree essentially with our own. With the exception of a review of our article Besredka[24] has not mentioned our work in his publications; several months, however, subsequent to the appearance of our article, he became convinced[25] of the existence of two substances in horse serum, one of which sensitizes (sensibilisogène) and one of which intoxicates (antisensibilisine). He further conceives this "antisensibilisine" as causing intoxication by uniting with a "sensibilisine" of the horse serum and not with the substance which sensitizes. His theory of the mechanism of anaphylaxis although agreeing in part with our own is founded on evidence to us inconclusive. Vaughan and Wheeler have independently determined the presence of two substances in egg white by a method of chemical separation. The work both of Besredka and of Vaughan and Wheeler[31] will be considered more in detail in the following article by Gay and Adler.

Since our consideration of the mechanism of serum anaphylaxis several articles have appeared which contain facts of direct bearing on this phase of the question. Otto,[6] himself still a staunch advocate of the antibody hypothesis, has with great impartiality reviewed and corroborated our work and in addition to further advances in our knowledge of transferred anaphylaxis, has raised certain very logical objections to his own hypothesis. We shall consider first of all these objections to the antibody hypothesis which he admits, before detailing our study on the single objection which he has logically been able to raise against our hypothesis.

The "reaction of fixation" of Bordet and Gengou,[8] which was devised by these writers in their earlier studies on immunity, was used in the first place to prove the presence of specific antibodies against bacteria in the case of certain "antimicrobial" sera which cause no bacteriolysis in vitro. It was later found to be of a clinical diagnostic value even superior to the Widal test in cases of typhoid fever by Lesourd[9] and in cases of cerebrospinal meningitis by Cohen.[10] . It depends essentially on the fact that the complex, immune body plus antigen has the power to absorb the alexin (complement) of fresh serum, the absorption or non-absorption of the alexin being proved by the absence or presence of hemolysis in subsequently added, sensitized * blood corpuscles; thus if one of the two factors, antibody or antigen, is known to be present, the existence of the other factor may be determined. The wide applicability of this test has further been shown by its use to prove that a given organism is the cause of a disease, as in the case of the bacillus of whooping-cough, described by Bordet and Gengou,[11] in which case the bacillus (antigen) reacted only

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* That is, corpuscles treated with a specific, inactivated hemolytic serum.

with the blood of children suffering from the disease. The test has been further employed to prove the existence of antigens or antibodies of different nature than bacteriolytic or hemolytic antigens or immune bodies. Thus it has been shown that the interaction of precipitogen and precipitin with or without formation of a visible precipitate also fixes alexin (Gengou,[12] Gay,[13] Moreschi,[14] Neisser and Sachs.[15] *) Very recently Nicolle and Pozerski [16] have shown that the toxins of tetanus and diphtheria, each in presence of its respective antitoxin, will form alexin-fixing combinations. The reaction of fixation has also been asserted to take place in mixtures of cancer emulsion and the serum of cancerous patients by Lüdke.[18] The now generally accepted methods of diagnosis by this reaction introduced in the diagnosis of tuberculosis, syphilis, and general paresis by Wassermann and Bruck,[19] Wassermann and Plaut,[20] and others may be mentioned. The reaction of fixation is, then, the most reliable and delicate diagnostic means of detecting an antibody in the presence of an antigen, or *vice versa*, and, so far as we know, is without exception.

According to Otto the reaction of fixation is lacking in combinations of horse serum and the blood of guinea-pigs sensitive to horse serum. We have also failed to obtain a reaction of fixation, but inasmuch as Otto offers no protocols of his experiments we offer herewith our experimental data with explanation of controls.†

Experiment 1. — On the same day were bled sensitive guinea-pigs No. 40 and No. 11 for ten cubic centimeters each (No. 11 was then given five cubic centimeters of horse serum intraperitoneally and reacted violently). A normal guinea-pig was also bled. The separate sera were heated the next day to 56° C. for thirty minutes. The serum used as "alexin" in the following experiment was from a normal guinea-pig bled three days previously and kept at room temperature. Two identical series of tubes were prepared as follows (numbered 1 to 15; and 16 to 30 respectively):

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* It is of interest to note the most ardent acceptance on the part of adherents of the Ehrlich school, of a method first used by Bordet to prove the unity of the alexin.

† We are aware of the recent assertion of Nicolle and Abt[17] that the reaction of fixation *does* take place between horse serum and the serum of sensitive guinea-pigs, but in the absence of all data from them we unreservedly emphasize the assertions of Otto and ourselves to the contrary.

1.	Serum, sensitive pig No. 40, 56°,	.1 cc.;*	horse serum,	.01 cc.†
2.	“ “ “ “ “ “	.05 “	“ “	.01 “
3.	“ “ “ “ “ “	.02 “	“ “	.01 “
4.	“ “ “ “ “ “	.05 “	“ “	.02 “
5.	“ “ “ “ “ “	.1 “	NaCl	.5 “
6.	NaCl	1. “	horse serum,	.02 “
7.	Serum, sensitive pig No. 11, 56°,	.1 “	“ “	.01 “
8.	“ “ “ “ “ “	.05 “	“ “	.01 “
9.	“ “ “ “ “ “	.02 “	“ “	.01 “
10.	“ “ “ “ “ “	.05 “	“ “	.02 “
11.	“ “ “ “ “ “	.1 “	NaCl	.5 “
12.	“ normal guinea-pig, 56°,	.1 cc.;	horse serum,	.01 “
13.	“ “ “ “ “	.05 “	“ “	.01 “
14.	“ “ “ “ “	.05 “	“ “	.02 “
15.	“ “ “ “ “	.1 “	NaCl	.05 “

To Series 1 to 15 was then added fresh guinea-pig serum, .05 of a cubic centimeter (diluted in NaCl solution to equal in volume .5 cubic centimeter).

To Series 16 to 30 was added fresh guinea-pig serum, .02 of a cubic centimeter (likewise equal in volume to .5 cubic centimeter). Contact between these mixtures was allowed for five hours at room temperature. To each tube, 1 to 30, was then added .5 of a cubic centimeter of a five per cent suspension of sensitized rabbit's blood (blood previously treated with the inactivated serum of a guinea-pig immunized against rabbit blood [20 cubic centimeters 5 per cent blood + 2 cubic centimeters serum guinea-pig > rabbit No. 3, 56°]).

In Series 1 to 15 the hemolysis of the added blood was complete in all tubes with uniform rapidity within one hour at 37° C In Series 16 to 30 the hemolysis was uniformly marked as "nearly complete" after two hours at 37° C., and the same note was made the next day, after conservation at 0° C. There is, then, in mixtures of the serum of sensitive guinea-pigs ranging from .1 to .02 of a cubic centimeter in amount, and horse serum (.01 or .02 of a cubic centimeter), no evidence of a reaction of fixation even with such doses of alexin as are not sufficient to produce complete hemolysis in the controls.

Another experiment, prepared under similar conditions, but with larger doses of the two sera in question, gave identical results.

Experiment 2. — The preparation of the factors concerned in this experiment is precisely as in the last experiment.

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[*] Made by dilution with NaCl solution (.85 per cent) to equal in all doses one cubic centimeter in volume.

[†] Made by dilution with NaCl solution to equal .5 of a cubic centimeter in volume.

1.	Serum, sensitive guinea-pig No. 41, 56°,	.5 cc.;	horse serum,	.05 cc.*
2.	" " " " " " "	.3 "	" "	" "
3.	" " " " " " "	.1 "	" "	" "
4.	" " " " " " "	.5 "	NaCl	.5 "
5.	NaCl	1. "	horse serum,	.05 "
6.	Serum, normal guinea-pig 56°	.5 "	" "	" "
7.	" " " " "	.3 "	" "	" "
8.	" " " " "	.1 "	" "	" "

In the first series (1–8) .05 of a cubic centimeter of guinea-pig alexin was added. In an identical series (9–16) .03 of a cubic centimeter of the same fresh serum was added. After five hours of contact at room temperature, .5 of a cubic centimeter of sensitized five per cent rabbit blood was added, and hemolysis was complete in all tubes within fifteen minutes. The subsequent addition of a second .5 cubic centimeter of the same sensitized corpuscles to the same tubes gave an eventual complete hemolysis in all tubes except 3, 5, and 8 (and corresponding 11, 13, and 16), in which tubes there was little or none; it is of interest to note that these tubes were the ones containing the most salt solution, the presence of which had undoubtedly allowed the more rapid and complete fixation of the free alexin on the first sensitized corpuscles added, leaving little or none for the second corpuscles. The point of importance to us, however, is the fact that there is *absolutely no evidence* of the fixation of the guinea-pig alexin in these mixtures of sensitive guinea-pig serum and horse serum.

Two additional series, each with tubes 1–8, were also made on the same day, and to one of these series was added .05 cubic centimeter of rabbit alexin, and to the other series .075 of the same serum. The resultant hemolysis of sensitized guinea-pig blood (treated with inactivated rabbit > guinea-pig hemolytic serum, and carefully washed to prevent subsequent precipitate formation, and restored to five per cent suspension before adding), showed in each series a *slight inhibition* of alexic activity in the mixtures of *normal* guinea-pigs' serum and horse serum, but no evidence of a reaction of fixation between the sensitive pig serum and horse serum.

By this most delicate reaction method, a method which shows, so far as is known without exception, the presence of antibodies of various natures (antitoxins, immune bodies, both hemolytic and bacteriolytic, and precipitins) no antibodies to horse serum can be demonstrated in the blood of guinea-pigs sensitive to horse serum. Otto has also stated that there is no diminution of alexin in the blood of sensitive guinea-pigs intoxicated by horse serum, which proves in

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[*] Total volumes of each factor the same as in last experiment.

addition that there is no evidence of a reaction of fixation in vivo.

That there is no combination of an antibody and antigen formed by the interaction of the serum of sensitized guinea-pigs and horse serum in vitro, which is toxic, at least for normal guinea-pigs, was shown by the experiments of Rosenau and Anderson, and of ourselves, as already cited. Otto has further stated very briefly that the blood of intoxicated guinea-pigs is not toxic for normal guinea-pigs. This statement, if true, would rule out definitely the formation of a new toxic substance by interaction of antibody and antigen, toxic at least so far as normal guinea-pigs is concerned; that such a substance might be formed and be toxic only for the properly prepared cells of the sensitive guinea-pig is a logical possibility. Let us consider these questions in turn and in detail by the following experiments:

Experiment 3. — A sensitized * guinea-pig was given five cubic centimeters of horse serum intraperitoneally; after severe symptoms for thirty minutes the animal was bled without anesthetic from the carotid and heart; the blood was rapidly defibrinated and kept at approximately body temperature until used. One and one-half cubic centimeters of the defibrinated blood of the above intoxicated pig, a few minutes after taking, was injected into the heart † of a normal guinea-pig (four hundred grams). No serum symptoms.

Experiment 4. — Two sensitive guinea-pigs were injected each with five cubic centimeters of horse serum intraperitoneally. When very sick (fifteen to twenty minutes) they were bled in turn, as in the last experiment, and the blood defibrinated. A normal guinea-pig was bled from the carotid for five cubic centimeters, and four cubic centimeters of the intoxicated, defibrinated blood was carefully injected into the same carotid cephalad. No symptoms, and when the animal was chloroformed an hour later no lesions were found.

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* By sensitized guinea-pig is indicated a normal animal of from 150–300 grams, which has received .01 of a cubic centimeter of horse serum at least two weeks previously. The sensitivity of each lot of pigs was proved by intoxicating one of the animals before using its fellows as "sensitive." Although the sensitivity has been shown not to disappear for several months or years, in the majority of instances it was possible to combine experiments so that a parallel animal could be intoxicated on the very day on which a "sensitive" animal was bled or used as such without intoxication.

† The method of heart inoculation, while in no instance endangering the animal's life, has been abandoned by us after careful trial. In the majority of instances it was found, by killing the animal a few hours after injection, that, although it may have shown no distinctive symptoms of any sort, the pericardium contains a large blood clot. Our experience has been with ordinary hypodermic needles.

Experiment 5. — Two sensitive guinea-pigs were intoxicated as in last experiments, and when symptoms were marked (forty-five and twenty-five minutes respectively) were bled as before. Within a few minutes six cubic centimeters of this blood was injected into the peritoneal cavity of a small (two hundred grams) guinea-pig. No symptoms.

Experiment 6. — Sensitive guinea-pigs Nos. 16 and 18 were given each five cubic centimeters horse serum intraperitoneally and during severe symptoms (fifteen and twenty-five minutes) were bled to death. Blood defibrinated, mixed and kept warm. Normal guinea-pigs received this "intoxicated" blood as follows: No. 49 (five hundred grams) given two cubic centimeters of blood into right jugular; No. 50 given three cubic centimeters of blood into jugular. No symptoms. When chloroformed after five hours no lesions were found in either animal.

Experiment 7. — Sensitive guinea-pigs No. 24 and No. 37 were given each five cubic centimeters of horse serum intraperitoneally. During severe symptoms they were bled (twenty and forty-five minutes). Blood defibrinated and kept warm. A few minutes later normal G.P. No. 62 (about five hundred grams) was bled from left carotid for eight cubic centimeters, and four and one-half cubic centimeters of the mixed defibrinated blood of the intoxicated pigs was injected into the left jugular vein. No symptoms, and, when chloroformed four hours later, no lesions were found.

It is evident from these experiments that the blood of sensitive guinea-pigs intoxicated with horse serum, and bled at different times during symptoms, has no toxicity for normal guinea-pigs, even when injected directly into the circulation in as large amounts as four and one-half cubic centimeters. As we have already mentioned there is the possibility that there might be a combination formed in the blood of the intoxicated animals, which although not toxic for the tissues of normal guinea-pigs, might yet prove so for the properly "prepared" cells of the sensitive animal. The only difference in such an interpretation from our own would be that such an action on the sensitized cells would be indirectly by the horse serum and not directly as we believe to be the case. Such indeed might experimentally seem to be the case from the following experiment were it not for the added control:

Experiment 8. — Under this experiment are collected data obtained at different dates but for simplicity grouped here under one heading. Defibrinated blood was obtained as in the last experiments from sensitive guinea-pigs which had been intoxicated with horse serum, and were undergoing severe symptoms.

Nov. 22, 1907. A sensitive guinea-pig was given one cubic centimeter of intoxicated blood into the heart. Slight symptoms.

Nov. 25, 1907. A sensitive guinea-pig was given one cubic centimeter of intoxicated blood into the heart. Marked symptoms. Recovered.

Dec. 18, 1907. Sensitive guinea-pig No. 15 was given one and one-half cubic centimeter of intoxicated blood into the heart. Slight symptoms.

Sensitive guinea-pig No. 17 was given, of the defibrinated blood of a *normal* guinea-pig, which thirty minutes previous to bleeding had received five cubic centimeters of horse serum intraperitoneally and had shown no symptoms, one cubic centimeter into the heart. *Distinct symptoms* as marked as in No. 15.

It is evident from this experiment that the blood of intoxicated guinea-pigs is indeed toxic for properly sensitized guinea-pigs, but as is shown by the control it is toxic not on account of any new combination of horse serum plus hypothetical "antibody," but on account of *free horse serum* in the blood of the intoxicated animal.

There is, indeed, but a single experiment which has seemed to offer positive evidence for the presence of antibodies to horse serum in the blood of sensitized guinea-pigs. As has been noted we were the first to point out that the injection of normal guinea-pigs with small amounts of the blood of sensitive guinea-pigs leads in two weeks to an active sensitization, as we interpreted it, of the new animal. These results were soon corroborated, and doubtless arrived at independently, by Otto.[6] Lewis[7] later corroborated both our results and also certain additional findings of Otto which are as follows: Otto found that not only will the blood of sensitive guinea-pigs in small amount lead at the end of two weeks to a sensitization of normal animals, but, if given in larger amount, produce sensitization in three days, two days, or even twenty-four hours. This production of sensitivity in a day he very reasonably asserts to be due to a "passive transfer of antibodies," and thinks that our results obtained after the longer interval are due to the same reason. Lewis compromises, and admits that the two-week sensitization, on account of the small amounts employed, is due to a horse serum "rest" (our anaphylactin); he believes, however, that the one-day sensitization is indeed a "passive transfer." In our experiments and in those of Otto and of Lewis the blood was transferred for the most part subcutaneously; this fact would, at first glance, best explain why in Lewis' experiments better results were obtained after two or three days, for, as is known, some such time is necessary for the absorption and distribution of antibodies from the subcutaneous tissue into the circulation. Dehne and Hamburger[21] have shown in man that the absorption of subcutaneously injected antitoxin is never complete in twenty-four hours, but reaches a maximum in from two to three days. J. Henderson Smith[22] has considered this subject even more attentively and determined the time when several different antibodies (agglutinins, antitoxins to tetanus and diphtheria) are to be found in maximal amount in the blood of man, goat or rabbit after subcutaneous injection; his results emphasize the slowness of absorption from the subcutis or even from the peritoneum, and agree as to the height being reached on the third day; he therefore counsels intravenous injections in treatment.

We have been able to corroborate the experiments of Otto and of Lewis as regards the rapid transfer of sensitivity to normal pigs; that this transfer, however, rapid as it is, is no passive transfer of antibodies becomes evident in view of our further experiments. If this transferred sensitivity were indeed due to a passive transfer of antibodies the maximal result with a given amount of transferred blood would, of course, be reached by injection directly into the blood vessels of the normal animal, and results depending on this transfer would be most evident as soon as the circulation had diffused whatever new product had been transferred. It is evident from the following experiment that no such rapid result follows, but *that a period of reaction* is always necessary to produce sensitivity in a normal animal after transfer of blood from a sensitive animal directly into the circulation.

Experiment 9. — Sensitive guinea-pigs No. 25 and No. 39 were bled from the carotid and the blood defibrinated.

Normal guinea-pigs Nos. 62, 63, 64 (weights about four hundred grams) were then in turn bled for approximately five cubic centimeters from the carotid, and there then was injected slowly into the jugular of the same side five cubic centimeters of the defibrinated blood of the above sensitive animals. (This operation is found to present no great difficulties if the animal is previously bled so as to reduce the blood pressure, and the cannula needle inserted into the vein is small and connected with the syringe by means of a flexible rubber tube. An assistant is necessary.) These three animals showed no marked effect from the operation and were given seven cubic centimeters of horse serum into the peritoneal cavity at the following times: No. 63, three hours after receiving sensitive blood; no symptoms. No. 62, three days after receiving sensitive blood; marked symptoms. No. 64, six days after receiving sensitive blood; marked symptoms.

Let us accept for the moment the fact, evidenced by this single experiment, that the rapidly transferred anaphylaxis requires a definite period of incubation or reaction. It is evident, then, that we have to deal with no passive transfer of antibodies, else the reaction would be most marked directly after transfer into the circulation. It is certain that the tissues of the animal must in some way react to the injected blood, containing the unneutralized anaphylactin of horse serum which (although it produces as we have shown a more complete sensitization at the end of two weeks) has already produced some sensitivity within twenty-four hours. In other words, this one-day transferred sensitivity is only a lesser state of our two-week transferred sensitivity. That a foreign substance (anaphylactin) may increase the assimilating property of the cell, which is the gist of our theory, and in the same short space of time as in the above experiments, is very neatly proved by the closely analogous instance recently described by Calmette, Breton and Petit.[23] These authors have shown that if a normal rabbit be given tuberculin intravenously it will give the typical ophthalmo-reaction to tuberculin after sixteen hours.

That the rapid transfer reaction of Otto is identical with the transferred anaphylaxis of Gay and Southard, but evidenced after a shorter interval than we had deemed probable, and that this reaction is simply an evidence of active sensitization on the part of our anaphylactin, is rendered certain by the following experiments. It will be remembered that we noted in the case of our transfer experiments that the sensitivity in the inoculated animals tested at the end of two weeks was much more evident with a given dose of "refractory" pig serum than with the same amount of sensitive pig serum; it will further be remembered that a refractory pig is one which has received at first much more horse serum than the sensitive pig and obviously by this process has retained more anaphylactin; that such an animal will react to horse serum only after a long period of incubation we explained by the necessity of a longer time to eliminate from the cells the assimilable elements of horse serum injected in the large initial dose or doses. It may be shown experimentally that the short-period transferred sensitivity likewise succeeds better if refractory pig blood is used, but that here also a distinct reaction period is necessary even after intravenous injection.

Experiment 10. — Refractory guinea-pig No. 3 * was bled to death and the blood defibrinated.

Normal guinea-pigs were treated as follows:

G.P. No. 45. Given 4.5 cubic centimeters refractory pig's blood, into the jugular.

G.P. No. 47. Given 4.5 cubic centimeters of blood of refractory pig blood intraperitoneally.

G.P. No. 46. Given 4.5 cubic centimeters refractory pig blood intraperitoneally.

Subsequent treatment: G.P. No. 45. Forty minutes after injection given .05 of a cubic centimeter of horse serum into the heart. No symptoms. (This animal was killed four days later and showed no lesions except a healed scar in left auricle No evidence of hemorrhage into pericardium.)

G P. No. 47. Twenty-four hours after injection, given 05 of a cubic centimeter of horse serum into the heart and fifteen minutes later five cubic centimeters of horse serum intraperitoneally. Distinct paralytic symptoms. Recovered.

G.P. No. 46. Five days after injection given five cubic centimeters of horse serum intraperitoneally. Severest prostrating symptoms. Recovered.

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* In each instance where a pig was used as "refractory" another pig previously treated in the same manner was given horse serum and shown not to react.

In this experiment on account of slight differences of treatment only pigs No. 47 and No. 46 may strictly be compared. The increased sensitization of five days over one day is marked in these two animals, however.

Experiment 11. — Refractory guinea-pigs No. 34 and No. 35 were bled and the blood defibrinated, mixed, and kept warm. Normal guinea-pigs were treated as follows:

G.P. Nos. 52, 53, 54. Given each three cubic centimeters of refractory blood into the left jugular.

G.P. No. 55. Given three cubic centimeters refractory pig blood subcutaneously.

Subsequent treatment: G.P. No. 52. Three hours after injection given five cubic centimeters of horse serum intraperitoneally. No symptoms. Chloroformed after eighteen hours; no lesions.

G.P. No. 53. Twenty-two hours after injection given five cubic centimeters of horse serum intraperitoneally. No symptoms.

G.P. No. 54 and No. 55. Three days after injection given each five cubic centimeters of horse serum intraperitoneally. No. 54 (jugular) showed severe, and No. 55 (subcutaneous), distinct symptoms.

This experiment would indicate by comparison with experiment No. 9 that refractory pig's blood sensitizes better in the short interval than does sensitive pig's blood; and also that the subcutaneous injection of refractory pig's blood is less quickly sensitizing than the intravenous.

To demonstrate conclusively the relatively higher sensitizing power of refractory pig's blood over sensitized pig's blood the following experiments are added in tabulated form:

Experiment 12. — Normal guinea-pigs received subcutaneously the amounts of sensitive or refractory pigs' defibrinated blood noted; and on the third day were given five cubic centimeters of horse serum intraperitoneally.

Pig No.	Treatment.	Symptoms on Inoculation of Horse Serum Three Days Later.
33.....	3.5 cubic centimeters sensitive blood.	Distinct, but moderate.
34.....	3.5 cubic centimeters sensitive blood and twenty-four hours later 3.5 cubic centimeters sensitive blood.	Distinct, but moderate.
35.....	3.5 cubic centimeters refractory pig's blood.	Severe symptoms.

Experiment 13. — Normal guinea-pigs received of sensitive or refractory pigs' blood subcutaneously, the amount indicated in the table, and, after three days, were each given five cubic centimeters of horse serum intraperitoneally.

Pig No.	Treatment.	Symptoms on Injection of Horse Serum.
56.....	4 cubic centimeters sensitive blood.	Very severe. Recovered.
57.....	2 cubic centimeters sensitive blood.	Distinct.
58.....	1 cubic centimeter sensitive blood.	No symptoms.
59.....	4 cubic centimeters refractory blood.	Severe. Recovered.
60.....	2* cubic centimeters refractory blood.	Slight, if any.
61.....	1 cubic centimeter refractory blood.	*Marked.*

A comparison of the symptoms in pigs No. 58 and No. 61 is particularly to be noted.

Still clinging to the logical possibilities of the antibody hypothesis, which in the face of the evidence we have presented can scarcely be further maintained, it might be well to inquire how the rapid sensitization of normal animals by the blood of refractory animals can at all be accounted for. In the instance of the longer period transferred anaphylaxis, if one admits this to be an instance of active sensitization, it is evident that the refractory pig's blood would contain more anaphylactin than does the blood of sensitive pigs, and so transfer better. Might it still be possible to explain the superior rapid transferring power of refractory pig's blood on the antibody hypothesis, admitting for the moment that other evidence supported this hypothesis? These refractory pigs, as we have defined them, are always bled at least two weeks after the last injection, in other words they are bled at a period favorable for such antibodies as are formed, and, as we have shown, precipitins to horse serum are often present; if these refractory animals possess antibodies to which anaphylactic intoxication might be due they certainly possess them in a greater amount than do the sensitive pigs. Since refractory guinea-pigs are temporarily non-reactive to horse serum but become so later on, this condition, on an antibody hypothesis, might be explained as an excess of antibodies, and the sensitive condition as due to an optimal minimum of the same antibodies. If this were the true explanation the bleeding of refractory pigs, thus removing mechanically some of the antibodies, might cause them to become sensitive at an earlier period. Experiment shows, however, that no such effect occurs.

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* In this animal at least one-half the blood escaped after injection.

Experiment 14. — Four sensitive guinea-pigs had been used for another experiment and on receiving five cubic centimeters of horse serum on the same day had reacted with more or less symptoms. Eleven days later one of them was given five cubic centimeters of horse serum intraperitoneally and showed no symptoms; another one was bled from the carotid, on the same day, for six and one-half cubic centimeters, and one hour later also given horse serum in the same manner and amount and showed no symptoms. On the sixteenth day a similar pair bled and unbled were given horse serum; both showed distinctive symptoms, the unbled animal reacting more violently than the bled one.

There seems, then, no reason to believe that the change of a refractory to sensitive state is due to the lowering of antibody content to a certain optimal minimum.

Certain of our experiments on the bleeding of sensitive animals offer strong presumptive evidence that the intoxication by horse serum is in no way due to the presence of hypothetical antibodies in the blood of the sensitive animals. If there were any such substances in the blood of sensitive animals we should expect that the abstraction of a relatively large amount of blood from them at least to reduce the severity of the symptoms on subsequent injection of horse serum. In the following experiment are grouped the results of such treatment on several sensitive animals performed at different times.

Experiment 15. — 1. Sensitive guinea-pig No. 26 was bled on February 1 for six cubic centimeters from the carotid. Given five cubic centimeters of horse serum on February 25 intraperitoneally. Severe symptoms. Recovered.

2. Sensitive guinea-pig No. 29 was bled for ten cubic centimeters from the carotid on February 27, and on March 10 given five cubic centimeters of horse serum intraperitoneally. Very severe symptoms.

In these two animals the question may be properly raised as to a possible regeneration of antibodies after bleeding. The evidence for such a regeneration is still in doubt; the results of Friedberger and Dorner[27] would seem to show that a severe bleeding leads to the diminution of antibodies. In the following animals no such objection can be raised since the animals were intoxicated soon after bleeding:

3. Sensitive guinea-pig No. 11 was bled on March 5, from the carotid for ten cubic centimeters, and one hour later given six cubic centimeters of horse serum intraperitoneally. Severe symptoms. Recovered.

4. Sensitive guinea-pig No. 27 was bled on February 27 for eight cubic centimeters and on March 13 for eight additional cubic centimeters; thirty minutes later was given five cubic centimeters of horse serum intraperitoneally. Very extreme symptoms and died in one hour. Hemorrhages cecum, kidney and lungs.

5. Sensitive guinea-pig No. 43, weight three hundred and ninety grams, was bled as much as possible from one carotid (12.5 cubic centimeters) and then given six cubic centimeters of the defibrinated warmed blood of a normal pig into the other carotid; and six cubic centimeters of NaCl solution into the peritoneal cavity. Rapid recovery. After sixteen hours the animal was given five cubic centimeters of horse serum intraperitoneally. Dead one hour; hemorrhages of lungs and stomach.

For the sake of completeness there may be mentioned at this point the result of a chemical study of horse serum by Gay and Adler, a full consideration of which is detailed in the following article. This study, although not ended, has shown that by means of fractional precipitation with ammonium sulphate a substance may be obtained (one-third saturation or euglobulins) which possess all the characteristics of a pure sensitizing substance without admixture of any of the toxic or assimilable elements. So far a relatively pure toxic substance has not been obtained.

DISCUSSION.

The theory of anaphylaxis which we offered a year ago as explanatory of the hypersusceptibility and intoxication of guinea-pigs brought about by horse serum, seems to us by the additional evidence from the continued study of this instance of anaphylaxis, and the literary evidence from other analogous instances, not only uncontroverted but more fully than ever justified. Increased susceptibility in the sensitized animal is due to the continued presence in the circulation of an unneutralized element of horse serum (anaphylactin) which acts as an irritant or stimulant to the body cells and in some way causes them to assimilate over rapidly certain other elements of horse serum. These assimilated or toxic elements are the same as those eliminated, without producing intoxication, during the incubation period following the first dose. This over-assimilation after anaphylaxis is the cause of the intoxication. This conception, although novel as applied to anaphylaxis, has, nevertheless, certain analogies. The "chemical messengers" or specific stimulating substances described by Bayliss and Starling[28] as "hormones" have many points in common with our anaphylactin. It has also been shown by Reid Hunt[29] that a well-known chemical substance, alcohol, will so stimulate the assimilating power of the body cells that the subsequent injection of acetonitrile, in doses harmless to a normal guinea-pig, will, in alcoholized animals, lead to so rapid an oxidation or cleavage of this product that the animal is poisoned; the striking analogy of this form of intoxication, involving as it does the intervention of two definite chemical substances, to the serum disease of guinea-pigs, is evident in the light of our hypothesis.

We were led to assume the existence of an unneutralized substance in horse serum (anaphylactin) which causes the sensitivity in treated guinea-pigs, because we found not only that the blood of sensitive animals, but still more so the blood of refractory animals would transmit sensitivity to normal guinea-pigs. Not only may this transmitted sensitivity be demonstrated two weeks after transfer, as we were first to show, but, if the doses are sufficient, it may be shown in a single day (Otto). That the substance in the blood of sensitive animals which causes sensitivity and transmits it to normal animals is not an antibody to horse serum, but some retained substance of horse serum is evident for the following reasons:

First, it is a characteristic of antibodies that they disappear rapidly from the blood unless the antigen is reinjected, and the sensitivity of guinea-pigs after a single minute injection of horse serum is present for months or years.

Second, the serum of sensitive guinea-pigs gives no "reaction of fixation" with horse serum. This reaction detects the presence of the smallest amounts of antibodies of various known varieties, and, so far as is known, without exception.

Third, although sensitivity may be transmitted in a day or so by the transfer of blood from a sensitive or refractory to a normal animal, this second animal, even when injected directly into the circulation, requires a distinct reaction period before becoming in turn sensitive.

Fourth, this rapidly produced sensitivity may be given to normal animals by the injection of a chemically separated fraction of horse serum (euglobulins), whereas whole horse serum in the optimum dose requires the ten-day incubation period. A similar rapid anaphylaxis is said to occur after the injection of tuberculin in rabbits (Calmette, Breton and Petit).

Fifth, the superior sensitizing power of a toxin-antitoxin mixture over normal horse serum, generally admitted and still further emphasized by a comparison of our present results with those of Otto or Lewis, cannot be accounted for on the ground of more antibodies to horse serum.

Sixth, the blood of refractory animals which temporarily are non-reactive, but which have received more horse serum than simply sensitized animals, transmits sensitivity better than the blood of these latter animals. This refractory condition, however, cannot be accounted for as due to an excess of "anaphylactic reaction bodies" for bleeding, and so mechanically abstracting such bodies, were they present, does not cause refractory animals to become sensitive.

That the intoxication of sensitive animals by horse serum is not due to a toxic substance, formed of an antibody plus antigen, and that moreover the reaction of intoxication takes place, not in the circulation of the animal but in the prepared cells, is evident because:

First, neither the blood of sensitive animals mixed with horse serum, nor the blood of animals undergoing intoxication is toxic for normal guinea-pigs when injected directly into the circulation. The blood of intoxicated animals is somewhat toxic for a sensitive animal, but owing solely to the presence of free horse serum in the blood.

Second, the abstraction of relatively large amounts of blood from sensitive animals (such as 12.5 cubic centimeters), whether or not followed by transfusion of normal blood, does not cause these animals to become less sensitive.

Third, acute cellular lesions in the nature of a fatty change occur regularly in sensitive animals on intoxication with horse serum. The localization of these lesions depends on the point of access of the serum to the circulation, and the rapidity with which these lesions may be formed depends on the rapidity with which the horse serum comes in contact with the cells. Two or three minutes at most will suffice under favorable conditions.

It is clear, then, that the sensitivity of guinea-pigs to horse serum is associated with the persistence of an unneutralized element of horse serum in the sensitive animal, and that the intoxication is due to some condition of the body cells which renders them particularly susceptible to those elements of horse serum that have been already eliminated from the first dose. The prepared condition of these cells might lead some to associate their sensitive condition with the "sessile receptors" of Ehrlich, and it is, therefore, well to point out that no such analogy exists. In the first place this sensitive cell condition depends entirely on the presence of an unneutralizable element, anaphylactin, which, by our definition, finds no "receptor" in the cell, and secondly, the entire "receptor hypothesis," as has recently been shown by Bang and Forsmann[26] and Landsteiner,[30] can be proved experimentally to be without foundation, as an explanation of reaction products. Bang and Forsmann have shown that the substance in blood which stimulates the formation of hemolytic antibodies in animals of another species, is chemically separable from the substance in blood which unites with these antibodies; the "receptors" or cell affinities, therefore, are not identical with the antibodies. It is evident simply that the cells of animals sensitive to horse serum have an increased assimilating, oxidizing, or cleaving power, which, when the serum is presented to such cells, is manifested by an over-activity indicated by the occurrence of fat. It would be purely speculative to consider the basis of the functional change in the cell which leads to this over-assimilating power, but we are by no means convinced that such changes may not some day be morphologically demonstrated.

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FURTHER STUDIES IN ANAPHYLAXIS.*

II. *On Recurrent Anaphylaxis and Repeated Intoxication in Guinea-pigs by Means of Horse Serum.*

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In a previous article[1] (1907) we have shown that the stage of "immunity" (Rosenau and Anderson, and Otto) or "anti-anaphylaxis" (Besredka and Steinhardt) which follows several moderate-sized injections or one large initial injection without intoxication, or which is present in animals after the intoxication caused by a second spaced dose of horse serum, is in reality not a state of immunity, properly speaking, but a refractory condition. The animals in this refractory condition contain no elements in their blood capable of neutralizing the toxic effect of horse serum, although their blood does contain, at times, other reaction bodies, such as precipitins. So far as they themselves are concerned as regards intoxication by horse serum, they are essentially in a condition similar to guinea-pigs which have just received a small initial dose of serum, for they eventually become sensitive to the toxic action of this serum; they differ from guinea-pigs sensitized by the small dose only in undergoing a longer period of incubation. The fact that animals who had received a single large initial dose, or several doses, showed an incubation period proportionate to the amount of serum injected was of importance in the evolution of our hypothesis, which insists on the

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presence of two substances in horse serum: the unassimilable anaphylactin which sensitizes and the assimilable elements which are gradually eliminated, and the subsequent ingress of which to properly prepared cells give rise to the intoxication. It is the presence of a large amount of assimilable substances, which naturally require time for their elimination, that, in the case of the large initial dosage, requires a longer period of incubation. A condition in the refractory animal of complete or nearly complete assimilation but of little or beginning elimination of the toxic element would account for the nonreaction of these animals to horse serum and explain why, at the same time, their blood on transference is more sensitizing for normal guinea-pigs than is the blood of sensitive guinea-pigs — since they have obviously much more of the anaphylactin, but little or none of the toxic substance of horse serum remaining unassimilated.

The point which we wish to emphasize in the present section is not that animals receiving a large dose of serum eventually become sensitive, but the fact that a sensitive animal intoxicated with a large dose, and recovering and thereby passing into a refractory state (antianaphylaxis of Besredka and Steinhardt), by the same mechanism again becomes sensitive to the toxic effect of horse serum. This fact has indeed already been evidenced in our own protocols and in those of other workers. We previously stated — "As may have been deduced from our observation of the refractory guinea-pigs and their eventual sensitivity, animals which have once suffered severe symptoms and recovered, if reinjected after a sufficient period, may be made to undergo again the typical serum intoxication. By a proper dosage the disease may be repeated at relatively short intervals and as frequently as desired."

It might be possible to draw an analogy between this form of recurrent hypersusceptibility, due indirectly to an intoxication, and the evidence of repeated intoxication in some diseases characterized by "crises" or repeated attacks, such as general paresis, epilepsy, and purpura, the only point of analogy which would be difficult to explain being the re-intoxication — which in this experimental disease of guinea-pigs is artificially induced. It is of advantage, however, to present concretely the protocols of certain animals that for the purpose of histological study have been intoxicated with serum two or three times.

I. Guinea-pigs showing secondary intoxication:

G.P. No. 46.	Jan. 2, 1907.	Given three cubic centimeters of horse serum subcutaneously.
	Jan. 17, 1907.	Given five cubic centimeters horse serum intraperitoneally. Slight symptoms. Recovered.
	April 9, 1907.	Given three cubic centimeters of horse serum intraperitoneally. Dead sixty minutes. Gastric and pulmonary hemorrhages.
G.P. No. 50.	Jan. 9, 1907.	Given 1.5 cubic centimeters serum of refractory guinea-pig "B."
	Jan. 24, 1907.	Five cubic centimeters horse serum intraperitoneally. Severe symptoms. Recovered.
	April 25, 1907.	Two cubic centimeters horse serum intraperitoneally. Dead in twenty minutes. Hemorrhages of heart, lungs, and stomach.
G.P. No. 47.	Jan. 2, 1907.	Given .01 of a cubic centimeter of horse serum subcutaneously.
	Jan. 17, 1907.	Five cubic centimeters of horse serum intraperitoneally. Severe symptoms. Recovered.
	April 9, 1907.	Three cubic centimeters of horse serum intraperitoneally. Dead one hour. Hemorrhages of lungs.

II. Guinea-pigs showing tertiary intoxication:

G.P. No. 37.	Dec. 24, 1906.	Given .01 of a cubic centimeter of horse serum.
	Jan. 10, 1907.	Given five cubic centimeters of horse serum intraperitoneally. Severe symptoms. Recovered.
	March 28, 1907.	Given one cubic centimeter of horse serum intraperitoneally. Slight symptoms.

G.P. No. 37.	April 25, 1907.	Given seven cubic centimeters of horse serum intraperitoneally. Distinct but moderate symptoms. Chloroformed four hours. Gastric and pulmonary hemorrhages.
G.P. No. 30.	Dec. 26, 1906.	Given .01 centimeter of horse serum subcutaneously.
	Jan. 8, 1907.	Given five cubic centimeters horse serum intraperitoneally. Severe symptoms. Recovered.
	March 28, 1907.	Given one cubic centimeter horse serum intraperitoneally. Slight symptoms. Recovered.
	April 25, 1907.	Given ten cubic centimeters horse serum intraperitoneally. Severe symptoms. Chloroformed four hours. Hemorrhages of stomach, lungs, kidney, liver.

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FURTHER STUDIES IN ANAPHYLAXIS.*

III. *The Relative Specificity of Anaphylaxis.*

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Rosenau and Anderson,[1] in their first article on the anaphylaxis in guinea-pigs produced by horse serum, considered the relative specificity of the reaction. They found that guinea-pigs which had been sensitized by a small dose of horse serum could be intoxicated after an interval of ten days by a subsequent dose not only of horse serum, but also to a less extent by serum from other animals; conversely, animals sensitized by other sera became more or less susceptible to horse serum. In each combination, however, a relative ("quantitative") specificity was to be noted, for in each instance the maximum reaction was obtained if the serum used for first and second injections was the same. These authors later[2] apparently showed that when protein substances of a more divergent origin are used the specificity becomes more apparent. Thus they showed that such substances as egg white, milk, and extract of peas, when given to guinea-pigs in successive spaced doses will cause intoxication on the second dose. According to the protocols of Rosenau and Anderson these different instances of anaphylaxis showed absolute specificity; that is, sensitization by milk, egg white, or horse serum was followed by intoxication only when the same substance which had sensitized was used for a second dose.

In a recent and most interesting article,[3] the same writers have continued their observations on this subject of the specificity of anaphylaxis. They have shown that if guinea-pigs be given a mixture of horse serum, egg white, and milk they become, after the proper period of incubation, susceptible to intoxication by each of these substances in turn, when

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administered on following days or even on the same day. It is well known that if a guinea-pig sensitive to horse serum recovers from a second dose of the serum, it immediately passes into a refractory stage and is unaffected by another dose of horse serum, for at least several weeks. This fact renders still more striking this serial intoxication with different substances after mixed sensitization with the same substances, and makes it seem that each reaction is, indeed, absolutely specific.

We have recently considered this question of the specificity of anaphylaxis, and our results, although agreeing in the main with those of Rosenau and Anderson, differ in essential particulars. In our hands the matter of specificity has been proved to be by no means absolute. It is clearly shown in the tables that follow that although an animal sensitized by a given proteid will react most violently to a second injection of the same proteid, it will frequently show distinct intoxication on injection of a proteid of different origin.

TABLE I.

These animals were given each one cubic centimeter of egg white (1 egg to 10 cc. NaCl sol.) subcutaneously as a first injection and at a subsequent injection were given the substances noted below.

G.P. No.	Interval.	Second Injection.	Resulting Symptoms.
154.....	16 days.	4 cc. egg white subcutaneously.	Moderate.
151.....	16 days.	5 cc. egg white intraperitoneally.	Dead 10 minutes.
112.....	35 days.	5 cc. egg white intraperitoneally.	Dead 20 minutes.
152.....	16 days.	4 cc. horse serum subcutaneously.	Slight.
150.....	16 days.	10 cc. horse serum intraperitoneally.	Severe.
113.....	35 days.	5 cc. horse serum intraperitoneally.	Dead 1 hour.
153.....	16 days.	4 cc. milk subcutaneously.	Suggestive.
149.....	16 days.	10 cc. milk intraperitoneally.	Doubtful.
114.....	35 days.	5 cc. milk intraperitoneally.	Distinct.

From Table 1 it appears that guinea-pigs sensitized with egg white react not only to egg white but very markedly to horse serum and less distinctly to milk. Under more favorable conditions, such as a longer period before intoxication, it seems indicated that the reaction to milk would be more notable.

TABLE 2.

These animals were sensitized with one cubic centimeter of whole milk subcutaneously.

G.P. No.	Interval.	Second Injection.	Resulting Symptoms.
80......	13 days.	5 cc. milk subcutaneously.	Distinct.
107.....	35 days.	6 cc. milk intraperitoneally.	Very severe.
81......	13 days.	5 cc. horse serum subcutaneously.	Marked.
110.....	35 days.	6 cc. horse serum intraperitoneally.	Very severe.
155.....	16 days.	10 cc. egg albumin intraperitoneally.	Doubtful symptoms.
108.....	35 days.	5 cc. egg albumin intraperitoneally.	Slight.

From Table 2 it is evident that guinea-pigs sensitized to milk will react on second injection not only to milk but quite as distinctly to horse serum; the reaction to egg white after milk is only slight.

TABLE 3 *a*.

These animals had received .01 of a cubic centimeter of horse serum subcutaneously as a first injection.

G. P. No.	Interval.	Second Injection.	Resulting Symptoms.
106	35 days.	5 cc. egg albumin.	Distinct but slight symptoms.
104	35 days.	5 cc. milk.	Doubtful symptoms.

TABLE 3 *b.*

These animals had received five cubic centimeters of horse serum subcutaneously as a first injection.

G.P. No.	Interval.	Second Injection.	Resulting Symptoms.
24	44 days.	7 cc. egg albumin intraperitoneally.	No symptoms.
48	28 days.	8 cc. egg albumin intraperitoneally.	No symptoms.
26	41 days.	7 cc. egg albumin intraperitoneally.	Doubtful.
29	28 days.	6 cc. milk intraperitoneally.	No symptoms.

Only the slightest indication of symptoms can be elicited by egg albumin or milk after sensitization by horse serum in the doses used. It is probable that, although under the conditions of sensitivity here given the animals are known to be highly sensitive to horse serum, the intoxication by the other proteids, which is only suggested, might be made more clear by a longer anaphylactic period or different initial dose.

A study of these tables shows that animals sensitized with either egg white or milk will react more or less characteristically to horse serum. It may also be seen that after sensitization with egg white guinea-pigs will react faintly to milk; and after sensitization with milk will react slightly to egg white. The reaction to egg white after sensitization with horse serum was noted as distinct in only one instance; the reaction to milk after horse serum was not to be noted in one instance and was doubtful in the other.*

A comparison of these different tables indicates in the first place that anaphylaxis is only relatively specific; and the fact that, in certain combinations (*e.g.*, sensitization with horse serum followed by milk or egg), an absolute specificity would seem to be present leads to correlative conclusions of interest. It is obvious that after sensitization by a given substance the maximum intoxication is caused by the same substance; we might refer to this as the "complete" intoxication; in addition there may or may not be "partial" intoxication by the other protein substances. It has been shown by our previous studies[4] that in the case of horse serum anaphylaxis, the substance of the serum which sensitizes (anaphylactin) is not identical with the substance which intoxicates. The distinction in these substances is brought out more clearly when we consider these instances of "crossed" intoxication. Horse serum has little or no power to sensitize against the other two proteids, while milk and egg have a more "general" anaphylactizing power; on the other hand, horse serum intoxicates readily after sensitization with one of the other substances, egg less readily, and milk still less so.

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*Since our results apparently refute the observations of Rosenau and Anderson on the specificity of these reactions we have accepted them only after repeated corroboration. As is indicated in the tables the animals tested for cross intoxication were put through in several separate lots. It is perhaps not gratuitous, in view of the small amount of horse serum which will produce anaphylaxis, to insist that the animals used not only had never themselves been previously used, but were the offspring of normal animals; the syringes used for the sensitizing dose, although they had been repeatedly washed, were boiled for from fifteen to twenty minutes before using.

When we consider the serial intoxication by the different proteids after sensitization by a single substance, either milk or egg, the relation of a "partial" to a "complete" intoxication is brought out more clearly.

TABLE 4.

These guinea-pigs had been sensitized by previous injection of one cubic centimeter of egg white sixteen days previously.

G.P. No.	Date.	Given	Result.
153	March 20, 1908.	4 cc. milk subcutaneously.	Suggestive symptoms.
	March 21, 1908.	5 cc. horse serum intraperitoneally.	Marked symptoms.
	March 23, 1908.	5 cc. egg albumin intraperitoneally.	Marked symptoms.
150	March 20, 1908.	10 cc. horse serum intraperitoneally.	Severe symptoms.
	March 21, 1908.	5 cc. egg albumin.	Severe symptoms.
152	March 20, 1908.	4 cc. horse serum subcutaneously.	Slight symptoms.
	March 21, 1908.	5 cc. egg albumin intraperitoneally.	Dead 30 minutes.
154	March 20, 1908.	4 cc. egg albumin subcutaneously.	Moderate symptoms.
	March 21, 1908.	5 cc. horse serum intraperitoneally.	No symptoms.

This table shows that even after "partial" intoxication has been caused in animals sensitive to egg white, by one or even by both of the other proteids in turn (G.P. No. 153) a succeeding set of symptoms may be elicited by egg white. When, however, egg white is used for the first (complete intoxication) further intoxication is not elicited by the partial intoxicating substance, horse serum (G.P. No. 154). Similar results are obtained after sensitization with milk.

TABLE 5.

These guinea-pigs had been given one cubic centimeter of milk thirteen days previously.

G.P. No.	Date.	Given	Results.
81	March 30, 1908.	5 cc. horse serum subcutaneously.	Marked symptoms.
	March 31, 1908.	5 cc. milk intraperitoneally.	Marked symptoms.
80	March 30, 1908.	5 cc. milk subcutaneously.	Distinct symptoms.
	March 31, 1908.	5 cc. horse serum intraperitoneally.	Doubtful symptoms.

It is evident from these two tables that if the protein substances are given in a properly chosen order, namely, partially intoxicating followed by completely intoxicating, that a series of intoxications may be produced after sensitization by a single protein substance as well as after combined sensitization with several protein substances.

When we come to consider the results of successive intoxications after the combined anaphylaxis due to injection of a mixture of several proteids, we find that they are no more absolutely specific than are the intoxications just detailed, obtained after sensitization by a single proteid. A careful study of the results obtained both by Rosenau and Anderson and by ourselves shows distinctly that, in the case of simple anaphylaxis followed by intoxication with the same substance, the combination egg followed by egg is most toxic, and serum followed by serum the next most toxic, while the combination milk followed by milk is least toxic of all. When we consider the resultant intoxication by a given proteid we must consider, first, the relation of the intoxicating substance to the anaphylactizing substance, that is, whether homologous or not; and secondly, we must consider what the absolute intoxicating power of each proteid might be if an anaphylactin which was common to all the proteids used could be imagined. Such a "common" anaphylactin is, of course, purely hypothetical, but we may approach a condition such as might be caused by such a substance, by means of the "mixed" sensitization of Rosenau and Anderson. If we sensitize guinea-pigs with a mixture of horse serum, egg white, and milk they become capable of giving the maximum symptoms of intoxication with any one of these substances. If, however, they are given each substance in turn it is found that the chain of successive symptoms depends on the order in which the proteids are given.

Table 6.

These guinea-pigs were sensitized by subcutaneous injection of a mixture composed of horse serum .01 cubic centimeter, egg white one cubic centimeter, and milk one cubic centimeter. They were subsequently given doses of five cubic centimeters of each substance in turn at intervals of twenty-four hours, and in each case in a different sequence. Nos. 117, 118, 119 were injected beginning on the thirty-fifth day; and Nos. 76, 77, 78 were injected beginning on the fifteenth day; the two series, however, were judged to be comparable inasmuch as the relation of order of substances was considered in relation to the intoxication by the other substances which preceded or followed. The first two intoxications of a series were given subcutaneously, and the last one intraperitoneally.

G.P. No.	Order of Intoxicating Proteid.	Symptoms Corresponding to each Proteid.
76.......	*Egg;* horse serum; milk.	*Marked;* distinct; no symptoms.
118......	*Egg;* milk; horse serum.	*Severe;* doubtful; slight.
119......	Milk; *egg;* horse serum.	Severe; *severe;* marked.
78.......	Horse serum; *egg;* ×	Severe; *dead thirty minutes;* ×
77.......	Milk; horse serum; *egg.*	Severe; marked; *marked.*
117......	Horse serum; milk; *egg.*	Severe; slight; *severe.*

This table is arranged to emphasize the relation of the order in which egg white was placed in serial injection to the resulting symptoms which it caused. A composite table of the different proteids showing the relation of their order of injection to the symptoms which they caused follows:

TABLE 7.

Order of injection on subsequent days.

Proteid.	First Day.	Second Day.	Third Day.
Egg	Marked. Severe.	Severe. Death.	Marked. Severe.
Horse serum	Severe. Severe.	Distinct. Marked.	Slight. Marked.
Milk	Severe. Severe.	Doubtful. Slight.	None. ×

A consideration of these tables shows that after what may be termed a sensitization common to serum, egg, and milk, the initial injection of any one of these substances, after the proper incubation period, will cause maximum symptoms. If injected on the second day egg alone will cause as marked symptoms as if given first; horse serum has already lost part of its potency to intoxicate if given after either of the other proteids; and with milk the loss is greater still. On the third day egg has lost none of its potency, horse serum most of its potency, and milk no longer intoxicates. It is evident that these substances may be arranged in order of their absolute toxicity, egg white, serum, milk, which corresponds to their apparent value after homologous sensitization. And what is more important still is the fact that if, after the mixed sensitization (serum, plus egg, plus milk), the weakest intoxicating substance (milk) is given on the third day it awakens no symptoms. This is clearly evident also in the tables of Rosenau and Anderson. In other words, the reaction which it might have evoked if given early in the order can be in no sense specific since it has evidently been fulfilled by the other two substances.

No particular reference is here made to the pathology and histopathology of the intoxications by egg white, milk, and the serial intoxications produced by injection of the three substances. The lesions caused by these substances differ in details from those which we have described in pure horse serum anaphylaxis and will be considered at another time.

CONCLUSIONS.

The anaphylaxis in guinea-pigs caused by the previous injection of any one of the protein substances, horse serum, egg white, or milk, is only relatively specific. The maximum reaction on second injection is always obtained when the substance which has sensitized is used, but in certain combinations intoxication can be produced by the other two substances. This intoxication, by a heterologous proteid is "partial" and does not occur if the "complete" intoxication produced by the homologous proteid has been effected; when partial intoxication has been produced by one or both of the heterologous substances, complete intoxication may still be effected by the homologous substance. The intensity of an homologous intoxication, after anaphylaxis by a single substance, would seem to depend somewhat on the substance used, the order of toxicity ranging, egg white, serum, and last of all milk. After combined anaphylaxis, produced by initial injection of all three substances, the first intoxication, allowing of course a proper incubation period, may be produced by any one of the substances in question. When intoxications are effected with each substance in turn the serial set of symptoms varies according to the order in which the substances are injected on the subsequent days. When injected as the second or third of the series, egg white alone produces maximal symptoms at all times; horse serum is diminished in toxicity if used after either egg or milk and has lost markedly if used after intoxication with both substances. Milk is very slightly toxic if given second in order and absolutely non-toxic if given third. This would compare with the actual toxic power of each substance as noted after homologous sensitization.

The mixed anaphylaxis, moreover, is only relatively specific since egg and horse serum will completely preëmpt the possibility of intoxication by milk if this substance is given last.

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FURTHER STUDIES IN ANAPHYLAXIS.*

IV. *The Localization of Cell and Tissue Anaphylaxis in the Guinea-pig, with Observations on the Cause of Death in Serum Intoxication.*

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1. The gross lesions of serum intoxication in the guinea-pig. — In 1907 we reported the occurrence of characteristic hemorrhages in guinea-pigs which had received a second properly timed dose of horse serum.[1] We observed such hemorrhages both in those guinea-pigs which died of the intoxication and in those which we killed at various intervals after intoxication. The hemorrhages were not quite constant in occurrence, but were found in one or more organs in thirty-four out of forty-one guinea-pigs autopsied at intervals within the first twenty-four hours after injection. The hemorrhages occurred in a great variety of organs. The most massive hemorrhages, and those most frequently observed, took place in the stomach wall. Thus we found gastric hemorrhages in thirty-two of the forty-one guinea-pigs examined within twenty-four hours of the toxic injection.

Further observations[2] bring our numbers to a total of eighty-six guinea-pigs with hemorrhages in one or more organs, five with doubtful hemorrhages, eleven without hemorrhages in a series of one hundred and two guinea-pigs examined within twenty-four hours of the toxic injection. Fifty-nine of these guinea-pigs (besides three doubtful) showed gastric hemorrhages. We have three new localizations of hemorrhage to report, the brain (three cases), the peritoneum (two cases), the spinal cord (one case).

Hemorrhages were localized in the complete series (1907 and 1908) as follows: Stomach, 59; lungs, 41; heart, 15;

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cecum, 9; spleen, 9; adrenal, 8; kidney, 4; muscle, 3; lymph node, 3; brain, 3; diaphragm, 2; liver, 2; pericardium, 2; peritoneum, 2; thyroid, 2; spinal cord, 1.

The occurrence of these gross lesions (in eighty-five per cent of our series of guinea-pigs) escaped the attention of the initial writers on anaphylaxis of this type (Otto in Ehrlich's laboratory, and Rosenau and Anderson in the U.S. Hygienic Laboratory). Otto, in fact, in his first paper [3] specifically denied the occurrence of macroscopic lesions in serum intoxication, and Rosenau and Anderson [4, 5, 6, 7] nowhere state the observation of macroscopic or other lesions in the disease. Lewis,[8] however, working under the direction of Theobald Smith is able to confirm our observations fully and states that Smith, one of the earliest observers of anaphylaxis of this type, had seen such lesions in intoxicated guinea-pigs several years before. Since these publications, there has been neither confirmation nor denial of these findings. Besredka [9] remarks that our structural findings may in the future be of service in clearing up the mechanism of the disease.

As we showed in 1907, these lesions have an important bearing on hypotheses concerning serum intoxication. We showed by an extensive histological study that the gross lesions are only indicators of a manifold series of cell-reactions, involving changes in capillary endothelium, voluntary and cardiac muscle fibers, nerve fibers, and gastric epithelium. As with the gross lesions, the microscopic lesions are distinguished by their focal distribution. This focality extends down to the separate cells, in such wise that single nerve fibers and single muscle fibers are found in a state of extreme or maximal fatty change in the midst of wholly normal fibers.

What is the significance of these lesions? The lesions cannot be regarded as anatomically specific for the serum disease. They belong in the same logical group with the multiple focal hemorrhages of the exanthems, of purpura, and of urticaria. They have much in common with hemorrhages due to local endotheliolysis produced by the application of such substances as venom. Can the reactions be proved by histological methods to show anything histologically or cytologically specific for the serum disease? This question must be answered in the negative. There is nothing in the lesions of this serum disease which approaches a tubercle or a small-pox vesicle in specificity. The importance of our structural observations does not consist in a demonstration of specific lesions, but in the exact demonstration of one method of producing lesions that are common in various types of disease, particularly in the exanthemata.

2. The cause of death in serum intoxication. — A complete delineation of this kind of pathogenesis would comprise: (1) modifications of tissue during the stage of preparation (anaphylactic phase), (2) the lesions of intoxication (critical toxic phase), and (3) the phenomena of repair and secondary anaphylaxis (reparative and secondary anaphylactic phases). In our former paper we confined ourselves largely to the lesions in the critical phase of intoxication, noting that the primary anaphylactic phase yielded few structural data open to observation. In the present communication we offer a continuation of our structural studies, embracing a more particular account of the cause of death in the critical phase, in the light of which some further observations on the anaphylactic and reparative phases are considered. Nothing is more striking than the sudden death following toxic injection by way of the carotid artery or jugular vein. The hemorrhages in brain, lungs, and heart, produced by such toxic injections, do not admit a purely mechanical explanation, since they are absent in control unused pigs injected with the same amounts of horse serum.

The local fatty changes in the capillary endothelium near the hemorrhagic areas in the heart muscle in these experiments must be closely related to the genesis of the hemorrhages.

But, although striking, these lesions are, in the strict sense, hardly lethal. What is the cause of death in the critical phase?

Hypotheses concerning the cause of death in the critical phase are in the field as follows:

1. *The functional hypothesis.* — Lewis[10] thinks the cause of death in the critical phase depends on "the disordered function of a single organ, or broken coördination between several organs." The hypothesis, as stated, gives no clue to the nature of the functional disorder, or to the organ or organs involved. Lewis leaves in doubt whether the intoxication affects the nervous system or the heart or the lungs, or the heart and lungs through the nervous system. The manifold lesions are admitted, but these lesions are not regarded as pertinent to the occurrence of the functional disorders. It does not appear that this hypothesis is more than a restatement of what occurs in the symptomatic course of the disease, or much more than a blank form for whatever might occur in the process.

2. *The latent brain lesion hypothesis.* — This hypothesis was constructed by Besredka and Steinhardt[11] at the outset of their work. They suppose that the sensitized guinea-pig acquires and retains a latent lesion in its brain. The toxic injection serves to start up (réveiller) the latent brain lesion, bringing about severe disturbances or death. If we substitute for the term lesion (with its structural connotations) the term condition (without such specialized connotations), it is evident that the hypothesis of Besredka and Steinhardt involves scarcely more than the assumption that the symptoms of death in the critical phase are effected through the specially sensitized brain. This hypothesis is, therefore, an advance upon Lewis' functional hypothesis in that Besredka and Steinhardt particularize the supposed source of the disordered functions. Although this hypothesis is not sufficient to explain the lesions of remote organs (such as stomach or cecum since described by us), the hypothesis may contain some truth in so far as it applies to some of the prominent and apparently fatal symptoms. The functional hypothesis of Lewis and the latent brain lesion hypothesis of Besredka have, therefore, much in common; but Besredka indicates

the single organ whose disordered function comes prominently into play.

3. *The hypothesis of specific toxic action upon the respiratory centers.* — There is no doubt that the cause of death is often a respiratory one. From such symptomatic observations, Rosenau and Anderson suggest that we here deal with a poison causing death through the nervous control of the respiration. In order to exclude local effects upon the diaphragm, Rosenau and Anderson [12] showed that the phrenic nerve after death is still excitable, and produces diaphragmatic movements on electrical stimulation after death. Vaughan and Wheeler,[13] dealing with similar considerations in poisoning by white of egg, also maintain that the poisonous substance owes its toxicity to a combination with the cells of the respiratory center. Rosenau and Anderson have since [14] generalized their original suggestion, proposing that "profound chemical changes, perhaps in the central nerve cells, are probably produced by the first injection." In a later paper [15] these writers further maintain that the phenomena of the critical phase are also explained by profound chemical changes, probably in the nervous system. It appears from this work, as well as from our own constant observation (see below) of pulmonary emphysema in those pigs which die rapidly, that the respiratory center, or, at any rate, the nervous respiratory apparatus, is prominently affected by the toxic injection. But, as appears from further considerations, this toxic action upon the respiratory center (or nervous apparatus) cannot be regarded as specific.

Briefly, then, the functional hypothesis of Lewis is scarcely more than a hypothesis in name, since it does no more than restate the problem; the latent brain lesion hypothesis of Besredka lacks a convincing demonstration of either the morphological or the chemical nature of the lesions, either before or after they are "réveillé" by the toxic injection; and the respiratory center hypothesis, as first advanced by Rosenau and Anderson, has considerable evidence in its favor, explains the direct cause of death in most or all instances, and merely errs in suggesting that the toxic substance is a specific respiratory poison.

Our work to the present time has shown that pulmonary emphysema is a constant feature at autopsy in guinea-pigs dying quickly after the second or toxic injection. We are inclined to regard this emphysema as the effective cause of death in the quickly fatal cases. Of course, the pulmonary hemorrhages and cardiac hemorrhages, which we were able to produce by toxic jugular injections with death in four minutes, are important factors as against possible recovery from emphysema in certain highly intoxicated guinea-pigs.

What is the mechanism of this fatal acute emphysema in the intoxicated guinea-pigs? The emphysema is an expression of death in the inspiratory phase with diaphragmatic spasm. All evidence at hand indicates that the diaphragm is under a constant nervous stimulation of excessive degree during the critical phase following the toxic injection. The probable course of the impulses which produce this hyperstimulation of the diaphragm is by way of the respiratory center in the medulla to the phrenic center in the cervical spinal cord and thence through the phrenic nerve.

Our recent experiments with sensitized guinea-pigs bring out the fact that the more readily the horse serum on the second injection can gain access to the nervous respiratory apparatus, the more certainly will excessive and spasmodic diaphragmatic and general respiratory contractions ensue. The fatalities upon injection of serum into the fluid spaces about the brain (we have preferred the post-orbital route for injection) and into the spaces about the spinal cord (notably in the upper cervical region) are very frequent, and with toxic doses of one cubic centimeter, practically constant.

We shall not here report in detail the results of all our localized inoculations with respect to their differential effects upon the nervous apparatus at large, reserving these findings for special neuropathological consideration. The effects of injections in the vicinity of various parts of the central nervous system are to a great degree differential, and may prove of some importance in determining special reactions of different regions, especially in the spinal cord. The effect upon the respiratory center is marked and early.

The simplest explanation of this effect is that the toxic factor of the horse serum in these local injections comes directly into contact with the properly sensitized nervous apparatus of respiration, and causes it to work excessively. As is well known, expiration is, under ordinary conditions, a purely mechanical matter; but inspiration is under nervous control. Excessive stimulation of the phrenic center leads to death in the inspiratory phase. Even after opening the thorax and excision of the heart and lungs, intense diaphragmatic contractions may be observed in guinea-pigs dying in the critical phase.

It has so far been impossible for us to determine which portion of the respiratory nervous apparatus is most highly sensitized, or whether any portion is more highly sensitized than another.

It is clear, however, that the hyperstimulation may in some instances be effected over two or three separate conducting elements or neurones. A striking experiment, recently accomplished, consists in the production of respiratory symptoms by touching the vagus nerve (lifted from contact with surrounding structures) of a sensitized pig with a pledget of cotton soaked in horse serum. The same procedure in non-sensitized pigs fails to evoke characteristic diaphragmatic contractions, and salt solution fails to produce the effect in sensitized animals.

This experiment would seem to indicate that the vagus nerve is to some extent sensitized in the general anaphylaxis. We have so far been unable to produce death by this procedure. Fatal issue seems to require immediate stimulation of the medullary or phrenic centers, and, so far, we are unable to report finally which of these centers is the more highly sensitized. Experiments to solve these questions are difficult, because it is desirable to avoid mechanical injury to the centers, but at the same time secure quick absorption of toxic serum by a given center, and distinguish the effects of the local anaphylaxis from those of anaphylaxis in the rest of the body which the serum speedily invades by blood or lymph.

Our vagus experiments may serve for the present to indicate the line of attack on the problems of local anaphylaxis and to bring out the mechanism of one of the most violent and striking of the symptoms of the serum disease. And our local injections with object of differentially intoxicating different parts of sensitized nervous system (to be reported in detail in a later study) serve simply to bring out the strikingly variable accessibility of the respiratory center, when properly prepared, to a poison injected at different points with relation to the nervous system.

Therefore we desire to substitute, for the theories of the cause of death in the serum disease as so far proposed, and above enumerated, a theory of local anaphylaxis of the respiratory nervous centers. By this we mean a condition induced in the respiratory centers, by means of anaphylactin in the fluid media bathing their cells, such that their elements are excessively stimulated when brought in contact with the toxic or assimilable factor of horse serum. The cause of death is, therefore, an indirect one, being founded on hyperstimulation of the phrenic nerve and cessation of respiration in the inspiratory phase. On this hypothesis the means of avoiding death in the critical phase of intoxication following anaphylaxis would be a therapeutic agent depressing the respiratory centers.

This hypothesis differs essentially from those previously proposed. So far from being due to a disorder of function or incoördination between organs, as proposed by Lewis, the cause of death would seem to be due to an excess of functioning of an apparatus, which is working quite properly in response to the stimulation it receives. The new hypothesis is also more specific than the hypotheses of Lewis and of Besredka. Nor is it necessary to suppose with Besredka a latent brain lesion which is started up once more by the second injection. Rather should we say that a condition had been induced in these cells, as a result of placing an anaphylactic substance in their surrounding media, such that certain results follow upon injection of a toxic substance. There is an essential difference between the idea of slight irritation followed by severe irritation of qualitatively the same character (as indicated by Besredka's metaphor, "réveiller") and the idea which we support that a substance (anaphylactin) bathing, among other structures, the respiratory nerve cells, has the capacity of altering those cells so that a second substance (normally ineffective) can become effective in stimulating them.

It is obvious that our hypothesis has much in common with any which supposes a specific action upon respiratory centers. And, if Rosenau and Anderson were to ground their hypothesis upon the rendering of these centers specifically accessible to certain toxic substances, we should agree with them. But it seems rather that they suppose that a specific toxine has been produced in the process of anaphylaxis or that a toxine is produced by the union of serum constituents and antibodies,[16] such that the wholly unaltered respiratory center can now be affected by this specific toxine. Whereas Rosenau and Anderson suppose a specific respiratory toxine to be somehow newly produced, we prefer to suppose that the anaphylactin of the first injection has altered certain properties of the cells.

Meantime, the insistence of Besredka upon "latent brain lesions" and of Rosenau and Anderson upon "profound chemical changes perhaps in the central nerve cells" is an indication that these workers fundamentally agree that we must look to the cells for the explanation of much of this problem. It does not seem that Rosenau and Anderson would be forced to hint at profound chemical changes in the cells, if the antibody hypothesis were quite convincing.

A consideration of the cause of death, with cessation of respiration in the inspiratory phase under the influence of respiratory central intoxication, which we can hasten by suitable application of serum near those centers, leads us, therefore, to the conception of a local acquired anaphylaxis or specific lowered resistance of these centers, under the influence of one substance (anaphylactin) so that they become hypersusceptible to another substance (toxic factor).

An extension of these conceptions to the rest of the body requires separate consideration.

3. Tissue anaphylaxis. — We have so far considered two striking features of the critical phase after the second injection, viz.: The multiple focal hemorrhages frequently found at autopsy within twenty-four hours of the toxic injection and the fatal issue which, when it follows, occurs usually within an hour of the toxic injection. We have not found that either of these features is absolutely constant, although our percentage of hemorrhages (eighty-five per cent) is enough to demonstrate their importance, although the fatal issue seems to vary, roughly at least, with the speed and volume with which the horse serum reaches some portion of the respiratory nervous apparatus. We shall later communicate work on the localization and dosage of respiratory central intoxication.

Is there some broader conception under which these two striking features of the critical phase can be united? Further work upon the histological features of the critical phase confirms the opinion expressed in our paper of 1907[17] that focal fatty changes are found in very numerous tissues of several different sorts. Some of these changes, especially when several altered cells are in close spatial relation, offer loci of lowered resistance permitting hemorrhages. But it is not at all necessary that the altered cells shall be so grouped as to allow hemorrhages. Take the stomach, for example, in which the most frequent and massive hemorrhages and hemorrhagic ulcerations occur: much more frequent than the hemorrhagic areas in these stomachs are areas in which fatty changes of sharply definite character but without hemorrhages are found.

The focal fatty changes of the critical phase are of more fundamental importance than the hemorrhages, which are possibly but the mechanical expression of *loci minoris resistentiæ*.

Since our former work, we have studied in particular the tissues of guinea-pigs in various stages of recovery from intoxication and during secondary anaphylaxis, as well as the conditions of second and third intoxications.[18] The result of this work has been to confirm the former findings and to show that the disease is essentially a critical one.

The toxic injection can be said to effect no further disturbance than that of the first hour. Though this could have been surmised from the symptoms, still it might be regarded as likely that some further phenomena would characterize the tissues.

We thought, in particular, that an investigation of the blood picture during the course of the disease might exhibit the tissue reactions more exactly.* This work so far indicates that the same type of reaction — hypoleucocytosis followed by hyperleucocytosis — occurs upon injection of horse serum into normal as into sensitized animals. This fact precludes extraordinary stress being laid at this time upon the leucocyte counts in this disease. The difficulty in drawing blood from guinea-pig ears during the critical phase is an interesting point, which may depend upon contraction of peripheral vessels due to an intoxication of the nervous system.

Although it is true that definite blood alterations do follow the toxic injection, it may be suspected that these alterations have to do merely with the elimination of horse serum and with readjustment of the blood cell supply and that they occur in normal animals in similar fashion after serum injections. A study of the spleens of the guinea-pigs, killed at various intervals of hours and days after the toxic injection, demonstrates that in less than six hours the spleen spaces become filled with polynuclear leucocytes. This tendency is so considerable that the spleens may become visibly swollen. This swelling is only in part due to congestion with blood corpuscles. The intrasplenic leucocytosis is prominent still in guinea-pigs killed at intervals up to twenty-four hours after the toxic injection, but in most cases gradually disappears and gives place to mononuclear phagocytosis during the third day. Some guinea-pigs on the fourth day yield little sign in their spleens of the toxic injection; but in some a moderate leucocyte destruction is somewhat persistent. But although a detailed study is contemplated of the conditions of the peripheral and splenic leucocytosis as well as of marrow conditions, it seems at present, from the orienting examinations already performed, that the relation of these pictures to the process of tissue anaphylaxis is quite obscure and that the body exhibits the same signs of eliminative effort in the blood after the first injection as after the toxic injection. In view of our study of recurrent anaphylaxis[19] in the same animal, these findings become interesting, but it is premature to state that the blood reactions have any relation to the process of anaphylaxis.

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* This was undertaken by Dr. M. M. Canavan of the Danvers Insane Hospital, who proposes to contribute the findings in detail shortly.

These studies may serve to show, therefore, that tissue anaphylaxis is very possibly not at all a function of the blood, detectable by cell changes therein. The reactions, both structural and functional, of the critical phase indicate that very numerous tissues of several orders have been altered in anaphylaxis.

What can be found in these tissues during the stage of anaphylaxis? It will be remembered that the only striking changes which we found in the anaphylactic phase in our former work were certain changes in the peripheral nerves and spinal cord, decidedly less often in nerve tissues above the medulla. These changes consisted in blackenings of scattered myelin sheaths demonstrable in Marchi preparations. The alterations were of two sorts, which we termed respectively linear and nodal changes. The linear blackenings, which exhibit the affected fiber as replaced by a row of black globules and signify a severe injury reparable only by regeneration, were decidedly less frequent than the nodal blackenings. The nodal blackenings, found in the peripheral nerves characteristically, show a limited osmic acid impregnation confined to the regions of Ranvier's nodes in a given fiber. These nodal changes are regarded as quite consistent with rapid recovery of normal conditions in the affected sheaths. It is possible that conduction is not interrupted by such changes but is altered in ways not now definable.

In addition to these myelin sheaths changes there are other and possibly correlative changes in nerve cells demonstrable by the Nissl method after alcohol fixation. We regarded these as within the limits of technical error, but, so far as reliable, consistent with prodromata toward the well known axonal reaction.

We were not eager to regard these changes as indicative of the latent brain lesions of Besredka or of the profound chemical changes of the nervous system proposed on theoretical grounds by Rosenau and Anderson, and, although we have worked much on this problem since and in particular with the sensitizing euglobulins of Gay and Adler, we are still unwilling to say that our findings represent the essential changes of the anaphylactic phase.

In the first place, we have found similar changes in seemingly normal material, and especially in the diphtheria toxone-paralysis material kindly given to one of us by Theobald Smith. It may be that these changes are simply indices of the extreme lability of nerve tissue, meaning by this lability a capacity for relatively rapid physical alterations of nerve cell and nerve fiber, demonstrable by osmic acid and methylene blue methods.

In the second place, our orienting work with the blood pictures in this disease indicates that to some extent the same species of leucocyte variation is present in the anaphylactic phase as in the toxic phase. So many substances are undoubtedly present in horse serum that the chance of changes effected by other constituents than the sensitizing or intoxicating constituents must be strongly considered. It is possible, therefore, that these anaphylactic nerve cell and fiber changes are purely incidental to the action of unrecognized constituents of horse serum.

Work is in progress with the relatively pure sensitizing substances (euglobulins of Gay and Adler) to discover what differential effects these substances may bring out.

One further word concerning the relation of the fatty changes and hemorrhages of the toxic phase and possible antecedent changes in the anaphylactic phase. Critics have suggested to us that possibly at some time during the anaphylactic phase fatty changes supervene in various foci in various organs, and that the hemorrhages of the toxic phase are simply mechanical expressions of local acquired weaknesses in the vessels. This hypothesis would suggest that horse serum can in the first instance produce qualitatively the same kind of visible changes which characterize the toxic phase. We have made further examinations of the tissues in large numbers of guinea-pigs. The anaphylactic phase is not characterized by such changes. Using the stomach wall as a histologically pure field for this study, we have yet to find, in any pig killed in the anaphylactic phase, convincing evidence of the presence of intraepithelial fat, vascular fat, or early necroses of epithelium under the influence of anaphylactin.

These statements may be generalized as follows: The essential cytological features of the process of anaphylaxis have yet to be discovered. They do not consist in a minor degree of those changes (focal cytolyses) which characterize the tissues in the toxic phase. The process of anaphylaxis is not a cumulative process, and the toxic phase is not the result of a summation of similar stimuli or effects.

Certain changes, expressive of the extreme lability of nervous structures, have been found in the anaphylactic phase in peripheral nerves and spinal cord. These changes may or may not represent essential features of the process of anaphylaxis. The nervous system is not a clear field, histologically speaking, for the study of minor fatty changes, since these may be the expression of numerous uncontrollable conditions. So far as the changes discovered have any bearing, the alterations produced by anaphylaxis may be regarded as of a physical nature, permitting speedy rearrangement of various contained substances.

Focal histolyses are not the rule in the toxic phase. Separate cells are more likely to be prepared for intoxication and to succumb thereto (focal cytanaphylaxis followed by focal cytolysis). But the diffuse changes in the stomach wall indicate that focal histanaphylaxis followed by focal histolysis may be the rule under some conditions (effect of gastric juice, etc.). Experience with the critical phase indicates that the cells of certain physiological centers may become highly sensitized (cell group anaphylaxis), and that the functional expression of their intoxication may lead to severe symptoms or fatal results.

4. The reparative phase and recurrent anaphylaxis. — We mentioned in our paper of 1907 that the serum disease might be repeated, and expressed the hope that by suitable repetitions chronic conditions would be produced. This hope has not been realized. The lesions do not necessarily repeat themselves in the site of the original lesions or even in neighboring situations. We have not carried our histological work beyond the reparative stages of tertiary intoxication.

Fresh intoxication in new sites is the rule in secondary or tertiary intoxications. But the repetition is virtually a new instance of the old disease and, certainly in the majority of instances, does not effect a cumulative action upon structures formerly attacked.

We hoped to find in the stomach instances of fresh intoxication superimposed on the remains of old and to discover that recurrent anaphylaxis would emphasize that of the sites formerly sensitized. The stomach seemed to be a likely seat for this cumulative anaphylaxis imagined by us, because of the tendency of the stomach to yield focal histolyses instead of the cytolyses of numerous other organs.

We thought that the new areas of local anaphylaxis might to some extent coincide with or overlap the old areas of histolysis and lead perhaps to chronic ulceration. But, so far, the conditions have not fulfilled such preconceptions.

This branch of the work, therefore, brings out indirectly the features of the anaphylactin hypothesis. It is the habit of the anaphylactin to sensitize focally certain cells or cell groups. The same anaphylactin in recurrent anaphylaxis is disposed to a similar focal sensitization in which, however, fresh elements are affected.

In those cases of cell group anaphylaxis, after which intoxication expresses itself largely in a functional manner (as in local respiratory center anaphylaxis), a repetition of similar toxic effects can be produced. There was no tendency for repeatedly intoxicated pigs to diminish the severity of their respiratory symptoms. It is possible that, on this line of attack, cumulative effects could be eventually demonstrated in certain centers. It is also possible that separate cells of the respiratory centers are always newly involved in recurrent anaphylaxis and repeated intoxication, and that the toxic effects are not due to activities of the same individual members of the cell group involved. These hypotheses, however, evidently transcend the range of immediate proof.

CONCLUSIONS.

The results of this work are in part confirmatory of our previous results and consist in part of novel data.

Eighty-five per cent of guinea-pigs which, after sensitization with horse serum and intoxication by a second dose of horse serum, die in the critical phase or are killed within twenty-four hours of the second injection, exhibit macroscopic hemorrhages in one or more organs. The stomach leads the other organs in frequency of involvement (fifty-eight per cent); the lungs stand next (forty per cent). Three unusual localizations of hemorrhage, not noted in our previous paper, are brain, spinal cord, peritoneum.

The cause of death, when it occurs, is respiratory. Respiration ceases in the inspiratory phase and shows itself anatomically and histologically as emphysema. Death does not occur, as a result of this disease, except in a critical phase which occupies at most one hour.

The most striking functional feature of the critical phase, after the second or toxic injection of horse serum, is severe diaphragmatic spasm. The spasms are often accompanied by similar shock-like spasms of the accessory inspiratory muscles and of other trunk and limb muscles.

The most rapid deaths are produced by intracarotid, intrajugular, post-orbital, and paraneuraxial injections. The occurrence and rapidity of death in the critical phase, as well as the severity of respiratory symptoms throughout the toxic phase, appear to vary with the nearness of the toxic injections to the respiratory central apparatus.

A new line of research is opened up by the paraneuraxial injections of horse serum in sensitized guinea-pigs. These seem to prove that differential irritative and paralytic reactions can be secured by small localized injections of horse serum adjacent to various parts of the sensitized central nervous axis.

Severe respiratory symptoms can be produced in sensitized (but not in normal) guinea-pigs by local applications of horse serum (not by salt solution) to the exposed vagus. This is interpreted to signify a conveyance of impulses over at least three neurones to the diaphragm, that is, to the medulla, thence to the phrenic center, and thence to the diaphragm. We have not produced death by these vagal applications of horse serum.

To explain these respiratory symptoms, we offer an hypothesis of local tissue anaphylaxis expressed in a relatively specific sensitization of the respiratory centers. We regard as unfounded those hypotheses which consider the respiratory (and other) centers and tissues as unaltered in the anaphylactic or sensitizing phase, and which allege the manufacture of antibodies in the blood serum which later unite with the second dose of horse serum to form new specific respiratory toxines. We regard this change induced in the respiratory centers as of a physical rather than a chemical nature, so far as this distinction is of importance in this connection.

Neither hemorrhage nor respiratory death is an indispensable feature of this disease. Some guinea-pigs show no hemorrhages. Some show slight symptoms. The hemorrhages do not vary in frequency or extent with the severity of the symptoms in all cases.

But all guinea-pigs so far examined in the toxic phase do show focal fatty changes in many tissues of several genetic types. These changes are, in many regions, of an extremely focal character, involving often a single muscle fiber, nerve-fiber, or other cell, as the case may be. The toxic phase is characterized by focal cytolyses of wide distribution. Except in areas of hemorrhage (where local mechanical destruction complicates findings) and in certain diffuse fatty changes in the gastric epithelium (where the local action of the gastric juice may come in play), groups of contiguous cells are not characteristically affected by fatty change: focal histolysis is not the rule.

And, if focal cytolysis (rather than focal histolysis) is the rule in the toxic phase, then it appears that the work of the anaphylactic phase is to sensitize cells in a variable degree (rather than to sensitize several contiguous or regionary cells in a like degree).

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XVII

TYPHOID MENINGITIS: CULTIVATION OF BACILLUS TYPHOSUS FROM MENINGES AND MESENTERIC LYMPH NODE IN A CASE OF GENERAL PARESIS, WITH NOTE ON EXPERIMENTAL TYPHOID MENINGITIS IN THE GUINEA-PIG.*

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I. We have to report a case of typhoid meningitis. The case presents certain unusual features. The bacillus typhosus was obtained in pure culture from the meninges and from a mesenteric lymph node, but was not present in the heart's blood at autopsy. There was no anatomical sign of typhoid fever except mesenteric lymph node swelling. The absence of typhoid lesions from the intestinal wall was especially noted by reason of the peculiar isolated lymph node swelling and was striking because the intestinal wall was actually thinner than normal. Such thinning of the intestinal wall is a not infrequent feature in advanced general paresis of the insane, of which the patient was a victim.

It appears that typhoid meningitis has occurred almost uniformly as an incident in typhoid fever of intestinal type. Every case of true suppurative typhoid meningitis with autopsy, as tabulated by Cole,[1] of Baltimore, has proved to be coincident with intestinal lesions. Cole has gathered twelve such cases from the literature and has added a thirteenth case from the Johns Hopkins clinic. Wentworth's case of a child of four years, from whose meninges the bacillus typhosus was cultivated by lumbar puncture, died, but unfortunately was not autopsied.[2]

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The present case might have given rise to the suspicion of a primary typhoid meningitis, had it not been for the positive mesenteric lymph node culture. We were led to the latter finding partly through noting the condition of the nodes at autopsy and partly through our study (not yet published) of infection with Bacillus coli communis along the same path. The present finding came as a surprise in a set of routine cultures from cerebro-spinal fluids and lymph nodes.

Not only was there no sign of typhoid fever at autopsy, but also during life the terminal symptoms were inextricably massed with phenomena of general paresis. The patient had for years been under medical care and no symptoms even remotely resembling those of typhoid fever had ever been noted. There were no gall stones. Unfortunately no Widal reaction was performed with the patient's blood either before or after death. The isolated organism was clumped by anti-typhoid rabbit serum 1–50,000.

II. Clinical history. — The details of the present case follow: A salesman of thirty-one was admitted to the Danvers Insane Hospital June 2, 1906, and died there Nov. 29, 1907. The patient contracted syphilis at nineteen. He married at twenty-two and had two children, still living. There were no miscarriages. Difficulty with bowels and bladder followed marriage. Patient was treated for bladder disease by Dr. Abner Post. At twenty-eight patient lost control of limbs and was confined to the house about two months, under the care of Dr. L. R. G. Crandon. Three months later he had regained partial control of his limbs, but had lost all control of his sphincters. After another month he had returned to work, but did not work steadily and seemed to have lost ambition. In the summer of 1905, his mind became obviously altered. He grew indolent and extravagant and given to buying expensive and useless articles. Loss of interest in things followed, together with loss of memory for recent events, lack of insight into illness, delusions of persecution by wife, irascibility followed quickly by crying. Before admission to hospital, he was euphoric, drawling and tremulous in speech, sprawling in penmanship, alternately depressed and exalted in manner. Knee-jerks were absent, gait ataxic, pupils stiff to light.

The family history was negative with respect to insanity. All the family are reported as nervous. A brother died of peritonitis at twenty-eight, a sister of pneumonia under twenty. Another brother and sister are living. Father and mother died of heart trouble at about sixty-seven and sixty respectively.

The patient was at high school one year and was a fair student. Considerable tobacco was used, and some alcohol. Intoxication denied. There was no history of typhoid fever or other acute disease.

The patient on admission was sallow, poorly nourished, and flat-chested, with a slight lateral curvature. There was slight dulness over right apex in front and in right upper back. Voice sounds were increased over right apex in front and over whole right back. The right chest showed bronchial respiration throughout. The respiration in front of right chest was of an interrupted character. The liver seemed moderately enlarged. The urine showed a very faint trace of albumin. There were a few small nodes in right groin and a scar on dorsum of penis.

NEUROLOGICAL EXAMINATION. — Slight swaying in Romberg position. Slight tremor of protruded tongue and extended fingers. Pupils irregular, left slightly larger than right. Left pupil reacted to light consensually, but not directly. Right pupil reacted very slightly to direct light, not consensually. Knee-jerks and Achilles jerks absent. Ankle clonus absent. Abdominal and cremasteric reflexes brisk. Sharp and dull points were recognized in the legs with numerous mistakes.

Vocal and facial tremor. Speech slow and drawling. Test phrases repeated well if care was taken. Consciousness clear. Orientation perfect. Calculating ability preserved. Many words omitted in writing. Penmanship clear but shaky. Hallucinations absent. Memory of recent events poor. Associations of a logical or defining type.

Patient denied various statements in commitment papers and had little or no insight into the mental side of his disease — slight euphoria.

After a month's observation the patient was removed to a quiet ward and set to work a few days in the scullery. One night he began to yell as if assaulted and said later that he had an idea that he was going to die. Before three months had passed he had become untidy, disorderly, and imperfectly oriented.

The general degeneration continued rapidly. One week before death the temperature rose to 103° F. and the patient succumbed to what seemed clinically like a bronchopneumonia. Unconsciousness two days before death.

Note with respect to history of typhoid. — Inquiries of his physicians, wife, employer, and brother tend to show conclusively that the patient never had a disease even remotely resembling typhoid fever.

CLINICAL SUMMARY. — Male without history of typhoid fever. Syphilis at nineteen. Marriage at twenty-two (two healthy children, no miscarriages). Disturbance of bladder and rectum. Successful in business (salesman) till twenty-eight, when advancing tabes confined him to bed for a time. At thirty mental signs of general paresis developed. Death at thirty-two after an acute illness of a week.

III.

The autopsy was performed sixty-seven hours after death by Drs. E. E. Southard and M. M. Canavan. Following is a copy of the protocol:

Well developed, emaciated white male; one hundred and sixty-five centimeters long. Lividity of dependent parts. Rigidity of limbs and neck. Pupils: left, 2.5 millimeters; right, four millimeters. Abdominal fat, one centimeter deep. Decubitus absent. Penis and scrotum show reddish discoloration.

Peritoneal cavity. — Walls not remarkable. Omentum thinly clad with fat. Mesenteric lymph nodes slightly enlarged, one measuring 2.5 x 1.5 x .5 centimeter. Diaphragm arches to fifth space on both sides.

Pleural cavities. — Both free from adhesions. Visceral surface of the *right* lower lobe shows delicate early fibrin, in small readily detachable strips. Pleural cavities contain a slight amount of fluid.

Pericardial cavity. — Slight excess of fluid. Pulmonary vessels give no evidence of ante-mortem clot.

Heart. — Weight, two hundred and ninety-five grams. Epicardial fat moderate in amount. Muscle firm and red, without evidence of increase of interstitial tissue. Endocardium of auricles and of right ventricle normal. Endocardium of left ventricle mantled with a thin layer of connective tissue, especially well marked towards the aortic valve. Valves normal, except mitral, which shows a few spots of yellowish softening both upon the edge and at various points in the curtain. Chordæ tendineæ normal. Chambers contain cruor clot. Coronary arteries show very faint, small areas of yellowish thickening, the most marked of which lies about two centimeters from the origin of the descending coronary.

Measurements: T. V., 11.5; P. V., 6.5; M. V., 7.5.
A. V., 7.5; L. V., 1.3; R. V., .4.

Lungs. — Weight, eight hundred and ninety grams, left; seven hundred and eighty grams, right. Edematous, congested, dark and semi-solid behind. The posterior portions of both lower lobes show areas in the midst of the congestion which are of a grayish pink color, and leave a granular surface on section. These measure from .5 centimeter to three centimeters in diameter. Pieces from the posterior portion of the lower lobe sink in water. A moderately foul odor from the cut surface of the lower lobe. Bronchi reddened and velvety. Vessels not remarkable. Bronchial lymph nodes small.

Spleen. — Weight, one hundred and eighty grams. Border shows numerous indentations. Capsule of the usual thickness. Substance not pulpy. Substance shows innumerable small oozing hemorrhages. Malpighian bodies somewhat larger than normal. Trabeculation not remarkable.

Gastrointestinal tract. — Esophagus not remarkable. Stomach small; walls thin and without rugæ. The remainder of the tract shows walls which are possibly somewhat thinner than normal, but show no other evidence of lesion. No lesion to correspond to the enlarged mesenteric lymph node was found.

Liver. — Weight, one thousand five hundred and eighty-five grams. Border sharp. Substance of the usual firmness, or a trifle increased. Lobulation distinct. Color grayish brown. Gall bladder normal.

Pancreas. — Of a pinkish color; gives no evidence of lesion.

Adrenals. — Show softened interiors.

Kidneys. — Weight, three hundred and fifteen grams. Capsule of the usual thickness, strips with considerable ease from a reddish gray surface. Cortex of normal thickness, shows in places slight grayish opacity, suggesting fat. Pelves contain a slight amount of slightly turbid fluid, but the mucosa shows no evidence of acute inflammation. Ureters normal.

Bladder contracted, with thickened walls. Ureteral orifices patent. Prostate not enlarged. Posterior portion of the right lobe contains a pea-sized abscess cavity from which wells up yellowish gray pus. The aortic arch shows a slight degree of sclerosis with faintly puckered lines radiating from a point opposite the coronary orifice. This lesion extends about six centimeters. The rest of the aorta is normal.

Head. — Skin exceedingly loose, and the whole skull cap thinned. The diplœ are absent. Adhesion with dura easily separated. The dura somewhat thickened, but not distended. Along the longitudinal sinus extensive calcareous granulations adhere to it. The longitudinal sinus does not contain blood, and the inner surface is normal in color. The pia is extensively thickened and opaque and a general subpial exudate exists which is more marked over the vertex where it lifts the pia from the brain surface to the extent of three centimeters in Rolandic, superior frontal, intraparietal, and mesial precentral sulci on each side. The arteries at base are free from atheroma. The temporal lobes are much bound down by adhesions, as is the cerebellum. Post-mortem softening is evident. The hemispheres show no asymmetry, but the frontal convolutions are markedly atrophic. The corpus callosum is united to the cortex by old adhesions and has to be dissected away from it. Lateral ventricles contain some slight amount of cloudy fluid, and the pia among vessels is opaque. Some granulations in ependyma. Brain weight, one thousand three hundred and five grams. Pons and cerebellum, one hundred and ninety-five grams.

Cord. — Dura much thickened, and the pia corresponds to its appearance in brain with a like exudate. Cross-section of cord shows sclerosis of posterior columns.

ANATOMICAL SUMMARY.

Acute conditions:

Hypostatic pneumonia, with early serofibrinous pleuritis and without lymph node swelling; enlargement of mesenteric lymph nodes; acute cerebrospinal leptomeningitis; multiple small hemorrhages of spleen.

Other findings:

Scar of penis; sclerosis of aortic arch (Heller's type?) and slight coronary arteriosclerosis; calvarium thin and dense; dura mater thickened and adherent to calvarium; calcified arachnoidal villi; chronic cerebral and cerebellar leptomeningitis; atrophy of frontal lobes; granular ependymitis; sclerosis of posterior columns of spinal cord; emaciation; unequal pupils; slight parietal fibrous endocarditis, slight mitral sclerosis; gastrointestinal atrophy; chronic cystitis; chronic abscess of prostate.

This picture seems to accord in most of its details (1) with the sequelæ of syphilis, (2) with the characteristic findings in general paresis of the insane, and (3) with a terminal acute condition.

IV. BACTERIOLOGY. — Cultures upon agar plates were made from the heart's blood, from the largest of the swollen lymph nodes, and from the pus of the subpial region of the vertex.

The heart's blood culture yielded a single colony, which proved to be Staphylococcus pyogenes albus. No further work was done with this organism, which is possibly related with the rich staphylococcal flora of the lung of this case.

The mesenteric lymph node and cerebrospinal fluid cultures both yielded many colonies of an organism which proved to be Bacillus typhosus.

The organisms identified as Bacillus typhosus are motile, Gram-negative bacilli, usually slender, though of variable size and length. They grow upon agar as moist white (bluish white, grayish white, occasionally slightly yellowish white) translucent (occasionally opaque) colonies, varying from pin-point to one millimeter in diameter. The organisms fail to produce gas on glucose agar, produce no indol, and do not liquefy gelatine. Milk is not coagulated, but becomes slightly acid. The acidity diminishes after five days. Growth on potato colorless.

Parallel cultures upon the same batch of media were carried out with known cultures of Bacillus typhosus, Bacillus coli communis, and Bacillus paratyphosus α and β, given us by Prof. H. C. Ernst. The organism of this case paralleled in all respects the known culture of Bacillus typhosus.

The serum of a rabbit immunized against Bacillus typhosus by Dr. F. P. Gay clumped our organism in dilutions as high as one to fifty thousand.

V. MICROSCOPIC FINDINGS. — The microscopic examination of the tissues added a few features to the anatomical diagnoses:

Slight pigmentation of heart fibers; pneumonia, staphylococcal, with bronchial plugs of bacteria; slight chronic splenitis; focal necroses of liver; slight chronic interstitial nephritis; slight cloudy swelling of kidney.

Following is the result of microscopic examination of tissues in trunk:

The heart showed, in a section through the wall of the left ventricle, a trivial degree of perinuclear pigmentation affecting occasional fibers only. Pigmented fibers are more frequent in the internal layers of muscle, adjacent to the thickened endocardium. The endocardial thickening is almost purely fibrous and mononuclear cells are conspicuously absent. No lesions like those figured by Mallory[3] (Plate LVII., Fig 18) were found, or any lesions pointing to the effect of typhoid toxines.

Sections from lower lobe of lung show a very rich flora of mixed character, dominantly coccal. Many alveoli appear to have served as culture tubes for the richest possible growths of cocci, often in chains. The bronchi are sometimes completely plugged with masses and sheets of organisms suggesting staphylococci. In the bronchi and in the middle of some alveoli the masses are possibly the effect of multiplication post-mortem. Phagocytosis for these bacteria by polynuclear leucocytes is rarely seen. A few bacillary forms were seen, but there is no evidence that they are typhoid bacilli. The question of phagocytic cells, the effect of specifically typhoid multiplication, as raised by Mallory in discussing a case of typhoid fever complicated by fibrinous pneumonia,[4] is not brought up in the present case. The phagocytic cells present are pigment laden. A few instances of cells phagocytic for red blood corpuscles were seen. There are a number of instances of small hemorrhages into the alveoli, and about these accumulations of blood corpuscles the growth of bacterial masses is especially rich. Fibrin is not a prominent element in the diffuse cellular and serous exudation, but may be found in a few places. There seems no reason for regarding this pneumonia as anything but a recent hypostatic pneumonia with very prominent bacterial picture, and certainly no reason for regarding it as of typhoidal origin.

The framework of the spleen, particularly in a zone beneath the capsule, consists of trabeculæ which are set unusually close, and the reticulum of the pulp in this region is prominent. The pulp spaces contain a moderate number of phagocytic cells, which contain as a rule blood corpuscles. The spaces are as a rule not unduly dilated. Lymphoid and plasma cells are moderately numerous, but polynuclear leucocytes are occasional only.. Giant cells of bone marrow type are rare findings. Fairly numerous ill-preserved mitotic figures occur in some parts of the pulp, perhaps in the plasma cells. The lymph nodules show no marked change. Small hemorrhages are prominent and frequent in the pulp. There are no organisms in association with these hemorrhages.

The liver shows a few focal necroses of the type described by Mallory[5] as characteristic of typhoid fever and ascribed by him to occlusion of liver capillaries by phagocytic cells derived chiefly from the spleen and intestine by embolism through the portal circulation. These necroses are in this liver infrequent. They occur in various parts of the liver lobule. The portal canals show in a few places evidence of accumulation of phagocytic cells, but neither these nor lymphoid and plasma cells can be considered as prominent features of the liver in this case. The fat content of the liver is low. There is small evidence of liver cell pigmentation.

The kidney fails to show the characteristic occlusion of veins in the pyramids with phagocytic cells, as described by Mallory in typhoid fever.[6] There are a few ill-marked foci of interstitial overgrowth in some parts of the renal cortex. Acute changes are represented only by a trivial degree of cloudy swelling and by destructive changes in a few isolated tubule systems (granular disintegration with tendency to formation of hyaline droplets). Some of the cells lining tubules of the pyramids contain collections of brown pigment granules.

The adrenal gland shows marked central and focal injection, a few foci of mononuclear cells in interstitial tissue, and post-mortem changes.

Prostate. — The walls of the abscess show great numbers of plasma cells. The interior shows numbers of very large phagocytic cells, containing chiefly fat. Some of the cells contain pigment. Polynuclear leucocytes are demonstrable only in relation to dead cells of some parts quite broken down. In certain places the destruction seems to have centered upon ducts and to be spreading outward therefrom; but in other places groups of plasma cells are found surrounding intact ducts. Corpora amylacea are abundant. Some intact bodies are found free in the interior of the abscess. No bacteria were demonstrated in the abscess.

Bladder. — No bacilli were demonstrable on the mucosa.

THE NERVOUS SYSTEM. — Tissues from many parts of the cerebrum and cerebellum, from the spinal cord, and from ganglia and nerves were examined by general methods and by the Weigert and Marchi methods.

The examination confirmed the clinical diagnosis of general paresis and of tabes, since there was not only an extensive chronic encephalitis, with the usual lymphocytic and plasma-cell exudate and irregular gliosis, but also a well-marked posterior column sclerosis, not unusual save in its extreme degree.

It might be surmised that some difficulty would arise in distinguishing the effects of paretic meningoencephalitis from those of the more recent typhoidal process. The well-known tendency of typhoidal processes to escape polynuclear exudation, at least until frank necrosis has set in, gave rise to the idea that the two mononuclear pictures — that of general paresis and that of typhoidal processes — might be confusing.

The picture presented by the meninges was scarcely what might be expected. Although numerous mononuclear phagocytic cells are everywhere found, yet the predominant picture is that of a polynuclear exudation.

The polynuclear leucocytes occur in greatest numbers in the tissue spaces, especially in the meshes of the lumbar arachnoid and in the spaces of the frontal and paracentral pia mater. In the lumbar region of the spinal arachnoid wide fields occur in which the cells are almost one hundred per cent polynuclear leucocytes. In places phagocytic cells occur, and in a few fields, even in the open tissue spaces, the number of phagocytic cells may rise to fifty per cent. Edema is a considerable feature in the meninges. Fibrin is found chiefly in the cerebral meninges and appears in numerous delicate strands in the tissue spaces.

One function of both large mononuclear and polynuclear cells seems to be phagocytosis for fatty materials. This can be well demonstrated by the Marchi impregnations, which show both types of cell to be fat-containing.

VI. Mallory suggested in 1898 that "careful bacteriological and histological study of the various complications of typhoid fever, and especially of cases of meningitis claimed to be due to the typhoid bacillus alone, may throw additional light on the character of the lesions produced by the typhoid bacillus."[7]

Mallory's histological evidence indicates that the essential lesion of typhoid fever is a proliferation of endothelial cells. The proliferation is diffuse but more marked in the lymphoid tissue of the intestine and mesenteric lymph nodes. The histological evidence points to the production by the typhoid bacillus of a soluble toxine. Mallory believes that this toxine is produced within the lumen of the intestine and diffuses along the lines of absorption through the lymphatics and along the lines of distribution through the circulation. Strictly speaking, therefore, the presence of the typhoid bacillus is not necessary within the tissues of the body for the production of the essentially typhoid lesions. The toxine alone could set up processes which, so far as we can see, might terminate in the same miliary necroses, due to endothelial-cell infarctions, that characterize typhoid fever as it occurs.

How then are to be explained cases of abscess, pneumonia, and meningitis, reported as due to Bacillus typhosus? Has the typhoid bacillus under some circumstances a truly pyogenic character? Mallory's material permitted the study of spleen abscesses and pneumonic lung in which the typhoid bacillus was present.[8] Study of the tissues inclined to the belief that the typhoid bacilli in the spleen abscesses had merely found there a favorable medium for growth and that the main effect of the bacilli in the pneumonic lung had been to complicate a lobar pneumonia with the proliferation of cells in the alveolar walls. The general conclusion is, therefore, that the typhoid bacillus has not been proved to be a pus-producing organism. The focal and purulent lesions of typhoid fever are either instances of infected infarcts due to typhoid toxine and subsequently invaded or occupied by bacteria (often by the typhoid bacillus itself) or else instances of focal lesions due to other causes than typhoid toxine and subsequently invaded or occupied by bacteria.

The position of typhoid meningitis is therefore almost crucial in this issue. With so simple a tissue as the meninges, as MacCallum[9] has again emphasized, the nature of the pure effects of the typhoid bacilli or their toxines should be made clearer. MacCallum has studied a case of typhoid meningitis coming to autopsy in the Johns Hopkins clinic. His conclusions follow the general trend of Mallory's argument. MacCallum finds nothing peculiar in the histological study of typhoid meningitis, unless it be the relative abundance of large phagocytic cells, found particularly about the veins, but also scattered through the tissues.

Although not studied in the light of Mallory's data, the cases of Ohlmacher[10] must be reviewed in this connection. Ohlmacher had reported in 1897 two cases of typhoid meningitis from the Cleveland City Hospital.

Ohlmacher's cases both died in the fourth week of recognized typhoid fever and both showed the usual intestinal lesions. The first case was delirious in the last week of life and several times passed urine involuntarily. In the second case there were no symptoms by which the date of meningitis could be fixed; the patient was either delirious or comatose throughout the thirteen days of his hospital stay. The descriptions of exudate found indicate the predominance in the first case and in parts of the second case of proliferated endothelial cells and mononuclear leucocytes. But one block from the first case was examined. Two blocks from the second case showed abundant and closely packed polynuclear leucocytes with fragmenting nuclei together with endothelial cells; a third block showed a predominance of endothelial and mononuclear cells, resembling the appearances of the first case.

The second of Ohlmacher's cases seems to have been severer than the first, since it showed an acute endarteritis. There are no notes in the cases indicating phagocytosis of the bacilli, which were abundant in the fibrinous and cellular exudate and in the lymph spaces of the first case and existed in countless myriads in dense lines in the meningeal lymphatics or scattered among the cells of the second case. It is noteworthy that the two regions of the second case which showed polynuclear leucocytosis were the regions which showed endarteritis.

It will be worth while to summarize MacCallum's findings, since his appears to be the first thoroughly examined case since Ohlmacher's.

Microscopic examination in MacCallum's case showed histological appearances identical throughout the cerebral, basal, cerebellar, and spinal meninges, varying only in intensity. Fibrin was considerably developed, but the picture is largely cellular. "In certain areas, apparently where the process is most intense, there are abundant accumulations of polymorphonuclear leucocytes. Here the disintegration of the tissues is most evident, and the leucocytes themselves are frequently fragmented and in an advanced stage of degeneration." MacCallum, however, regards these polymorphonuclear leucocytes as reacting to the typhoid infection and not as brought out chemiotactically by tissue necrosis.

Besides these foci of polymorphonuclear leucocytes, the meninges contained great numbers of mononuclear cells, among which are mentioned cells resembling lymphocytes, plasma cells, and all transitions from lymphocyte-like cells to certain very large irregular mononuclear phagocytes having a large vesicular nucleus and abundant ground-glass-like pink protoplasm.

The arteries showed lifting of endothelium by exudate in a form of arteritis not specific for typhoid meningitis but also shown in pneumococcus and streptococcus meningitis.[11, 12, 13] Hektoen's earlier work on tuberculous meningitis may be reviewed in this connection.[14]

It is the relative abundance of the large phagocytic cells which distinguishes typhoid meningitis from other forms. But, although attention has been focused upon the high content of mononuclear phagocytic cells in typhoid meningitis, the occurrence of these cells does not appear to us so remarkable as that of numerous polynuclear leucocytes evoked by Bacillus typhosus.

MacCallum's finding of polynuclear leucocytes in the meninges corresponds well with ours, but the cells in MacCallum's case occurred more in certain foci where disintegration of fixed tissues was most evident.

It seems, then, that the data of Ohlmacher's and MacCallum's cases as well as of our own point to the possibility that the typhoid bacillus, under certain circumstances and notably in the meninges, may act as a pyogenic organism. A case of purulent typhoid meningitis, recently reported by Henry and Rosenberger,[15] appears to resemble ours in the cell-contents of the meninges. This case is described as showing a large number of polynuclear and mononuclear cells, but the large phagocytic cells did not predominate.

With respect to this point it may be noted that MacCallum's case showed the course of a typhoid fever over three weeks long until death, complicated by cerebral symptoms at least two weeks in duration. Henry and Rosenberger's case lasted nine days. Our case had acute symptoms, probably due to bronchopneumonia, for a week, and unconsciousness lasted but two days. Moreover, whereas MacCallum's case, in common with most of those reported, possessed the usual lesions of typhoid fever, the other two cases are less easily to be pressed into the class of typhoid fever. The case of Henry and Rosenberger showed lesions possibly consistent with early typhoid fever (acute catarrhal enteritis with enlargement of Peyer's patches and mesenteric lymph nodes), but scarcely consistent with extensive toxic effects elsewhere. Our own case showed one feature in common with typhoid fever, enlargement of mesenteric lymph nodes, but there is little evidence that typhoid toxine has produced extensive effects in this case. It would seem simplest, therefore, to take the phagocyte-content as indicating roughly the duration of the disease and the degree of endeavor to rid the meninges of necrotic material. There seems to be very little evidence from any of these cases that the typhoid bacillus has produced in the meninges a special accumulation of phagocytic cells.

It will be remembered that Mallory's hypothesis concerning the specific proliferation of endothelial cells in typhoid fever maintains that this proliferation is due to the toxine of the bacillus and not to the direct action of the bacillus itself. Mallory could not demonstrate any relation between the situation of the organisms and the character of the lesions.

In typhoid meningitis we may be dealing not with the effects of typhoid toxine alone, but also with the direct effects of the bacilli themselves. Polynuclear leucocytosis in the meninges appears to be a more characteristic feature than the accumulation of large phagocytic cells.

VII. EXPERIMENTAL TYPHOID MENINGITIS IN THE GUINEA-PIG. — The hypothesis is raised, by a consideration of the data of Ohlmacher's, MacCallum's, Henry and Rosenberger's, and our own cases, that the typhoid bacillus may in the meninges produce an exudation of polynuclear leucocytes. This effect of the bacillus, if demonstrable, would be of a different order from the proliferative stimulus of the typhoid toxine, though the effects of both bacillus and toxine may be together visible in any one region, as a combination of large phagocytic elements and polynuclear leucocytes.

Since the issue in a fatal human case is clouded by possible preëxistent phagocytes and by the well-known tendency of the meningeal tissues to exhibit large phagocytic cells in every kind of tissue necrosis, it seemed desirable to see what the typhoid bacillus might do in a clear field.

The best results in this direction appear to have been obtained by Tictine[16] of Odessa, using rabbits, guinea-pigs, and susliks. Tictine trephined and made subdural inoculations. Abscesses at the site of inoculation were produced in rabbits.

Bacillus typhosus was recovered in the brain as late as twelve days after inoculation. Inflammatory edema occurred within twenty-four hours and suppuration within three days. The experimental meningitis of the suslik took a slower course than in the rabbit and showed marked individual variations. Bacillus typhosus was recovered from suslik brain as late as thirteen days after inoculation. The guinea-pigs used succumbed in twenty-four hours. Blood infections, as indicated by positive cultures in the spleen, were not infrequent in Tictine's animals.

In order to parallel results with work on other organisms[17, 12, 13] we preferred to use the guinea-pig. To avoid the direct effects of cerebral trauma we employed the method of orbital injection after cocainization, already employed in work with other organisms.[12, 13]

We have been able to recover Bacillus typhosus in small numbers from the base of the guinea-pig brain as late as ten days after orbital inoculation. The brain of a guinea-pig similarly inoculated and killed after fourteen days proved to be sterile.

Numerous colonies of B. typhosus were cultivated from the base of the brain five days after inoculation. Thereafter, if our series represents general conditions, the bacilli quickly diminish in number in the guinea-pig.

The same culture (derived from the present case) injected in small quantity into the peritoneum kills overnight, producing a profuse exudation containing polynuclear leucocytes. Such a guinea-pig contains B. typhosus in the heart's blood, but the brain is apt to be sterile.

On the other hand, with our orbital inoculations, we have in no case produced a septicemia with B. typhosus. Probably, therefore, our histological findings in the nervous system are not to be taken as phenomena of a general infection.

The histological study of tissues from a series of guinea-pigs inoculated by way of the orbit with B. typhosus shows that the lesions produced are mild though quite definite. In general it may be said that the critical phase of the disease produced comes later than with the pyogens studied in previous papers. The base of the brain from the fifth to the seventh day shows the most acute lesions, consisting in a diapedesis of blood globules and an exudation of polynuclear leucocytes, together with serum.

Inoculations with Micrococcus aureus, previously reported, showed the acute inflammation at its height in three days. The pneumococcus inoculations gave more variable and less acute lesions, in the sense that mononuclear elements are admixed with polynuclear leucocytes comparatively early, and the height of the polynuclear exudation comes about the fourth day. The streptococcus inoculations correspond in main features with the pneumococcus inoculations.

In the typhosus inoculations, mononuclear elements arrive in the vessels and in the pial meshes by the seventh day.

On the tenth day the exudate has diminished in quantity, the cells and albuminous materials are found fused together in a seminecrotic mass including pyknotic polynuclear cells, and the vessels no longer give evidence of the arrival of fresh exudative cells.

By the fourteenth day the disease is virtually past, and traces only of old exudate are found. Sections from various parts of the nervous system stained for fat (Marchi) demonstrate few or no fatty changes until the seventh day, but are thereafter demonstrable in considerable quantity throughout the decline of the exudative disease. At fourteen days there are still many fibers showing black markings, and at this time numerous cells phagocytic for fat have made their appearance. The most extensive blackenings occur in cranial nerves. Thus it is interesting that the locus of severe fatty change is identical with that of most voluminous cellular exudation, but the time-relations of the two processes differ, the fatty change running behind the exudation by some days.

Parallel inoculations have been made with B. coli and paratyphosus a and β. These will be reported in a comparative review at a later date.

VIII. CONCLUSIONS.

The points of the present paper are as follows:

1. A classical case of taboparesis, with previous history of syphilis, but without history of typhoid fever, succumbs after a week's acute illness to bronchopneumonia and to purulent cerebrospinal meningitis.

2. A typical strain of Bacillus typhosus was isolated in pure culture from a swollen mesenteric lymph node and from the meningeal pus. The blood failed to yield Bacillus typhosus. There were no typhoidal lesions in the intestines.

3. The meningeal exudation contained polynuclear leucocytes in great numbers. This finding, in connection with the older findings of Ohlmacher, W. G. MacCallum, and Henry and Rosenberger, leads to the hypothesis that Bacillus typhosus within the meninges may exert a directly pyogenic action. Should this hypothesis be upheld, the direct action of the bacillus stands in sharp contrast to the proliferative effects of the typhoid toxine described by Mallory in the intestine, lymph nodes and elsewhere in the viscera. The indications are, therefore, that Bacillus typhosus may have two separate effects, the one produced by a diffusible toxine (Mallory) characteristically in the intestinal tract and the other produced in the meninges either by direct local action of the bacilli or through an endotoxine, due to destruction of the bacilli.

4. In confirmation of the results of Tictine, Bacillus typhosus was experimentally found to inflame the meninges of guinea-pigs. In accordance with the hypothesis stated above, guinea-pig brains proved to show an exudation containing many polynuclear leucocytes. Mononuclear elements arrive by the seventh day after inoculation.

5. Research is desirable to determine whether the local action of Bacillus typhosus in the meninges is, or is not, of endotoxic type.

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XVIII

DEMENTIA PRÆCOX, PARANOID, ASSOCIATED WITH BRONCHIECTATIC LUNG DISEASE AND TERMINATED BY BRAIN ABSCESSES (MICROCOCCUS CATARRHALIS).*

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We present here the analysis of a case of delusional insanity. During life the case was thought to belong possibly in Kræpelin's group of dementia præcox. One main interest of the case lay in the fact that, by a little emphasis of certain features, the delusions could be regarded as of psychogenic origin, as a malignant elaboration of ideas following a personal disfigurement. There were, however, certain other features rendering a purely psychic origin doubtful for these delusions. Notable among these other features are the autopsy findings, which point to a somatic disease coincident in time with the mental disease, an obstinate lung disease with frequent periods of toxemia. Whatever conclusions are warranted from these features, the case is in itself interesting and, particularly in respect to the chronic meningitis and brain abscesses found at autopsy, presents some data requiring special consideration.

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I.

The subject of this history showed few peculiar or striking traits until the age of twenty-five, when, upon the Fourth of July, 1902, his face was disfigured by powder from a small cannon. Thereafter his mental attitude was altered and eventually developed into a picture characteristic of dementia præcox, but with delusions of negation. Meantime a chronic pulmonary disease, with multiple abscesses, was developing and giving rise to the suspicion of phthisis. In 1907 the patient died, was autopsied at the Danvers Insane Hospital, and showed chronic abscesses in many organs.

Of special interest was the discovery of multiple abscesses in the brain. The cell-contents of the meninges were such that a chronic meningitis, possibly dementia paralytica, might have been suspected.

A brother, two years older than patient, is living, in good health, without peculiarities. Patient's father, a nurse, still living, has no peculiarities. Patient's mother died in patient's early life in childbirth, having had poor health, fainting spells and dropsy during pregnancy. A maternal uncle died of tuberculosis. Both grandmothers are said to have died of paralytic shock, both grandfathers of gangrene of the foot. There is no suspicion of mental disease in the family. The family seems to have been American throughout.

The patient made good recoveries from ordinary children's diseases. Occasional headaches, for which no cause is known, affected the patient from eight to fourteen years of age. The patient attended public schools in New York until sixteen years of age, worked as errand boy and in other capacities until nineteen, and followed chair making (ten to thirteen dollars a week) until about the time of his accident. Pneumonia and pleurisy in early life, according to patient. Gonorrhea at twenty-three. No history of syphilis. The patient averred that he had drunk excessively (three to ten glasses of whiskey almost daily) for a number of years; no delirium tremens, no arrests. He is described as reticent, but usually cheerful. Unmarried.

July 4, 1902, patient was injured by the premature explosion of a cannon, and his face was blown full of powder. He was carried to the Cambridge Hospital (for access to whose records we are obliged to Dr. L. S. Hapgood), where he was operated on for traumatic cataract of the left eye. There is no record of mental change during his three weeks' stay at the Cambridge Hospital.

After leaving the hospital patient became rather depressed and worried over his disfigurement. The depression deepened. Patient became inactive and late in December, 1902, grew much worse, talked little, but said he was losing his reason and would never get well.

Jan. 5, 1903, patient was admitted to the McLean Hospital for the Insane. We are indebted to Dr. G. T. Tuttle for the following abstract of events till his discharge Feb. 20, 1903.

During his stay in the hospital he was at first much depressed, but gradually improved. At first he said he could not go out and meet people " as they all know " of his case, that he was " forsaken by everybody," that he was too weak to dress, that there was no case in the hospital like his. He was mentally quite clear, was perfectly well oriented, but seemed a little worried. He gave in detail the story of his illness, adding to the above that about two weeks before entrance he experienced a peculiar "lifting" sensation, and since then his feelings are different, his senses are gone, he has no affection for anybody. He thought that his masturbation was the cause of it all, and this was his principal worry.

During the first of his stay he was quite moody and depressed, but after the first of February he began to feel better in spirits, could think more clearly and began to take more interest in things about him. He improved from that time and for the last ten days of his stay he acted perfectly naturally, said that he wished to go home and that he felt able to go to work. At the solicitation of his brother he was allowed to go on a visit on Feb. 20.

Five days after discharge from McLean, patient tried to commit suicide by shooting in the head. He was committed to the Danvers Insane Hospital, March 17, 1903, where he stayed the remaining four years of his life.

The patient at Danvers was of extreme interest for two reasons, (1) on account of the nature and course of a lung disease (variously regarded as abscess and as phthisis), and (2) on account of the mental symptoms which reminded one of certain features in involutional cases.

The course of the somatic disease may be first considered. Upon admission the sequelæ of the Fourth of July accident were obvious in thickly studded powder-marks of face and ears and in corneal opacities of the left eye. Five punctured wounds, the result of patient's suicidal attempt, and a surgical incision above these wounds, were practically healed.

The lung showed dulness over right lower back and there was diminished expansion in this area. The patient was practically normal in other respects save that vision in the left eye was much impaired, the left knee-jerk was diminished, and the biceps, triceps and wrist reflexes could not be obtained. In certain lights the left pupil was larger than the right. There was not, at this time or later, any suspicion of exudative or degenerative brain disease. Although difficult to disengage from frank delusions, the patient's statement that he had been feeling poorly for months may reflect somatic conditions.

Possibly the symptomatic onset of lung disease may be put back in the latter part of 1902. At all events, the physical conditions noted in the chest on admission were quickly translated into symptoms. There was constant coughing. In less than a month after admission patient became extremely weak and coughed up first blood-stained, later muco-purulent, material. The dulness over right lower back found on admission persisted, and, indeed, lasted till death; but the upper part of the chest became dull also. Breathing was suppressed in the right lower back and harsh above.

Two weeks later the cough had subsided and the patient was up and about. The left back now showed diminished fremitus and breathing.

Ten weeks later (about fourteen weeks after admission) blood was again coughed up and the lung disease seemed localized in the right upper lobe. Occasionally the temperature rose to 104° without chill.

Such attacks were more or less frequent features during 1903–1907. Some of the examiners thought the case one of tuberculosis; others, lung abscess. Repeated examinations of the sputum for tubercle bacilli failed to show any, except a few upon one occasion in

1903. In view of the post-mortem examination, it seems best to regard this finding as accidental.

In December, 1906, patient had severe hemorrhages and brought up thick mucous. Although no tubercle bacilli could be found, the patient was placed in the building for tuberculous patients and ran a constant temperature of variable height. A week before death patient developed abscesses of left arm and of right great toe, containing foul, thick, dirty-brown pus.

In view of the clinical course of the case and the post-mortem findings described below, it seems that the chief features on the somatic side may be explained by fresh outbreaks of lung disease with invasion of greater and greater areas, finally involving the whole lung with abscesses and pneumonic reactions of various ages. The patient was toxemic at various times and may even have been septicemic at times, as at the close of life.

Turning to the psychiatrical side, we find a constant picture of depression, personal delusions of a self-accusatory and negating cast, with a tendency to delusions involving the rest of the world. Certain delusions about his viscera are not inconsistent with the somatic disease in progress. The mental picture varied in severity, and the symptoms came in the form of attacks, sometimes with katatonic excitement. The katatonic features of the case became more characteristic toward the last. During the toxemic periods due to the lung disease patient was quiet, but on questioning revealed depressive delusions having relation to his somatic condition.

The following notes from the clinical records (for which we are indebted to Drs. H. W. Mitchell and C. B. Sullivan) show these points more in detail.

Examination of March 18, 1903: Patient in all respects normal except for depressed emotional expression, which, however, was only appropriate to the delusive ideas centering upon himself and his unhappy condition. He said he had been feeling poorly for months and in December vowed he would give up drinking, but on New Year's day drank once more. "On New Year's day I had an awful time. Could not do anything. Came to the North Union Station and a flash came over my head. My brain was paralyzed. All my troubles left me and I have been no good since. My spirit was taken away and I don't know how I am to die. I have got no future. I feel awfully. Haven't been like other people since then. I can't work — got no power unless some one tells me. Couldn't even get bullets into my head because skull was thick and brain was small. I am the worst thing that ever lived, worse than a murderer. Given up by God — the lowest thing that can be." "I never was just right, but I didn't know enough to have any trouble. I thought I knew everything until I lost my spirit. I have always been a d—d fool. Worse than that; worse than anything could be." Irritability on leading questions about mental disease. Abject depression and weeping when speaking about himself.

Conversation March 25, 1903. "You never saw anybody like me. You can't understand my case. I was born different than any one else. I got no spirit of God. It's awful. I have got a good father and good folks, but there is no hereafter for me."

April 7, 1903 (about a week before a severe pulmonary attack), patient complained that his viscera had become changed, that he had coughed out his lungs, that his spirit had gone.

April 13, 1903. "I am dead, that is all there is about it. The dead can talk and move around in the world. Does it not say so in the Bible? Does it not say a dead man shall walk erect? I can stand every test for a dead man."

For months, and throughout 1904, patient was depressed, slow in movements, a little seclusive and failed to express spontaneously any delusions. He would sometimes agree that former ideas were delusions. He was sometimes comparatively cheerful.

Early in 1905 depression deepened, apprehensiveness, suicidal and "peculiar" ideas developed. Feb. 13, 1905, patient had a fainting spell, but got into bed before it came on, thought he was dying, and his heart seemed to stop. "Brain all gone, ran out through spinal cord, skin rotten, no sensation." On conversation agreed that his brain was not yet wholly run out, and appreciated that his ideas were morbid.

Feb. 15, 1905. "I haven't got good news for you to-night. The world is coming to an end. The devil has been pounding on the walls all day. It must have been the devil. Who else could it have been? I would like to go away and leave this world. The world is going to be burned up, it is so wicked, and he is the cause of it all." Patient also said about his somatic disease, "This is leprosy I am spitting up." When physician suggested that he prepare for death, he was quite willing for the event to occur at once. Patient thought McKinley's death was in some way due to him, having been so informed by God. Feb. 19, tried to commit suicide by choking. Thereafter grew retarded and disinclined to keep oriented for time and to think. Such depressive ideas as the following were prominent: that he was the cause of the end of the world, that the world is degenerating, that he is to be cut up and put down the hopper, that he is nothing more than manure.

March 8, 1905. Agitation, worry, slow anxious wandering about ward, weeping. " Seems as if everything I do is wrong, but I don't think it is." *Q.* " What is wrong ? " *A.* " Well, last night I didn't want to go to bed, and they had to take hold of me. There is Christ there in that last bed (pointing to a general paretic) and he can't help me." Then began to pray, saying: " Have mercy on us and help those who are afflicted and I have wronged, and I wish that I might have the devil taken out of me, and if there is any good in me that I might have life sometime and be washed out that I might have life sometime." Asked to whom he was praying says, " I don't know whether it is God or the devil. God is mighty over all."

April 13, 1905. Sitting in chair, apparently quiet, but on seeing physician, patient became agitated, said, " The world came to an end, and I am wild," began to grind teeth and snarl, tried to bite physician's hand lain on patient's shoulder, clenched fist, assumed an attitude as if about to spring, and, turning his head from side to side, said, " I can't stop this, I can't help it." Similar " wild beast " simulations came at intervals during two months. Occasional suicidal attempts by strangling.

Nov. 7, 1905. Kept left eye closed and left side of mouth drawn up, explaining mannerism by saying that he took medicine that entered eye. Orientation and memory perfect. Said he had passed both ends of the world and got behind everybody. "When I spit, it goes right back into my body again." "Somebody is bringing all the heavens down." "I am murdering the whole world and can't help it."

Occasional excited spells, with running up and down the halls and a variety of bodily contortions. The most common movement was a turning of body from left to right with a sudden jerking of head backward and a flow of irrelevant disjointed talk.

Throughout his bedridden condition in 1906–7 patient maintained orientation, memory and social relations very well and was little disturbed.

Thus, during his Danvers life, the delusions varied more in their spontaneous expression than in their qualitative content and were gradually growing severer and more comprehensive in the topics involved. Katatonic excitement was a feature in 1905, and a few mannerisms developed later. Peculiar contortions came in 1906. After December, 1906, the somatic disease got the better of the motor expression of patient's delusions. Further analysis may be deferred till the autopsy findings have been reviewed.

II.

The autopsy, forty hours post mortem, was performed by the writers. The anatomical diagnoses are as follows, arranged in groups so far as possible with dates of origin.

CHRONIC.

Bronchiectases of lungs, with *abscesses.*
Fibrosis of posterior half of right lung.
Bilateral chronic obliterative pleuritis.
Chronic fibrous auricular endocarditis.

Chronic fibrous pericarditis (milk patch of right ventricle).

Chronic gastritis.

Slight *aortic sclerosis.*

July, 1902.

Gunpowder granules in face and ears.

Corneal opacities of left eye and (slight) right eye.

March, 1903.

Scars of bullet wounds of right temple.

Bullet in right temporo-parietal suture.

Perforation of skull at pterion, with focally *adherent dura mater* and slight *localized leptomeningitis.*

Small old *lacerations of cerebrum* beneath intact inner table under imbedded bullet.

RECENT.

Abscesses of lungs.

Organizing pneumonic foci.

Acute pneumonia.

Swelling of bronchial lymph nodes.

Abscess of left forearm (surgical incisions).

Onychia of left hallux (surgical removal of nail).

Abscess of left chest.

Abscesses of kidneys.

Abscess of spleen, with local *acute peritonitis.*

Multiple abscesses of brain, involving

1. *Left second and third temporal gyri.*
2. Tip of *left occipital lobe.*
3. Tip of *right occipital lobe.*
4. Posterior half of *left cerebellar hemisphere.*

The details of the protocol follow: White male, 163 cm. long. Development good. Nutrition fair. Rigor mortis, general and moderate except in left elbow. Subcutaneous tissues of the upper third of the left forearm are infiltrated with pus, having a foul odor. Upon incision, pus is found to affect not only the subcutaneous tissues, but also the superficial muscles, but does not involve either the bones of forearm or the joints of the elbow. Two surgical incisions of the left elbow region of recent date. Onychia of one left hallux without involvement of bone. Nail of the left hallux has been removed surgically. The muscles of the left foot are less rigid than those of the right. The subcutaneous tissues of the face and of the anterior aspect of both ears are filled with powder granules. Depression with cicatrix, 3 m. in diameter by 0.5 cm. deep, lies at a point 3 cm. posterior to malar border of orbit and 3 cm. above zygomatic process.

Subcutaneous fat of abdomen 1.5 cm. deep. Subcutaneous fat in tissue overlying right second and third rib with intercostal muscular tissue show infiltration with pus which wells up from a small cavity into the muscular tissue from an abscess cavity in the lung tissue below.

Peritoneal cavity. — The free surface of the spleen shows a thin sheet of grayish fibrin of recent formation overlying an abscess cavity of the spleen tissue, but extending several centimeters beyond the region of the abscess. Beneath the peritoneum of the lesser cavity overlying the pancreas, at a point about midway of the body, is an abscess 1.5 cm. in diameter involving both subperitoneal tissue and pancreatic tissue.

Omentum moderately filled with fat. Appendix buried with adhesions. Intestinal tract not remarkable. Mesenteric lymph nodes not enlarged.

Pleural cavities. — Both obliterated by dense old adhesions which are firmest in the right back, especially in the middle and lower portion.

Pericardial cavity. — Not remarkable. Finger-nail-sized milk patch over right ventricle opposite the middle point of the intra-ventricular septum. Pulmonary arteries opened in situ show fluid blood and cruor clot.

Heart. — Weight, 245 gm. Muscle firm and red. Inner surfaces of auricles are of a brownish-gray color. Valves not remarkable. Pulmonary arteries normal. Chambers contain chicken fat and cruor clot.

Measurements: Tricuspid valve, 8.5; mitral valve, 7.0; aortic valve, 6.5; pulmonary ventricle, 11.5; left ventricle, 1.5; right ventricle, 1.5.

Lungs. — Left, 585 gm. Right, 635 gm. There is no portion of the lungs which fails to show exudate. Posterior and central portions of both lungs contain numerous abscess cavities which show gray, rough, shaggy walls and contain slightly creamy yellow pus. No extensive connection was demonstrated between the abscess cavities and bronchi. The lung tissue outside of the abscess cavities was dark red, moist and friable. The posterior half of the right lung is remarkably tough and is provided with an extensive surplus of fibrous tissue. Bronchi reddened. Pulmonary vessels not remarkable. Bronchial lymph nodes, swollen, but fail to contain foci of tuberculosis.

Spleen. — Weight, 235 gm. In the middle of the diaphragmatic surface of the spleen is a dark colored area of fluctuating consistence bearing a slightly grayish center, from which, with slight manipulation, pus may be made to well forth. On section the abscess is found to measure 2.5 x 1.5 cm. in diameter and to lie nearer the diaphragmatic surface of the spleen than to the hilus. The walls are rough and shaggy; the contents, creamy pus. The spleen substance in general is of grayish-pink color and very pulpy. The Malpighian bodies cannot be made out in the grayish-pink substance. Accessory spleen, 1.2 cm. in diameter, lies in connective tissue opposite the splenic flexure.

Gastro-intestinal tract. — Esophagus not remarkable. Stomach walls are thin and smooth. The rest of the intestinal tract is normal throughout, although explored carefully to discover ulceration.

Liver.— Weight, 1,765 gm. Border slightly rounded. Several so-called post-mortem ischemic areas are found, but no evidence of tuberculosis. Consistence slightly diminished. Color slightly translucent, grayish-pink. Gall bladder not remarkable.

Adrenals. — Show no evidence of focal lesion.

Kidneys. — Weight, 375 gm. Strip with abnormal ease. Substance was of a slightly opaque gray-pink color, generally suggesting the appearance of acute nephritis. Both kidneys show several abscesses, from 0.5 to 3.0 cm. The abscesses resemble those of the pancreas, lungs and brain, and are most numerous and extensive in the right kidney. Pelves, ureters and bladder walls not remarkable.

Testes thread well.

Aorta. — Shows a few punctate spots of yellow color along the border of the sinuses of Valsalva.

Head. — Covered by thick black hair. On the right side, two finger-breadths posterior to the orbit and on a level with it, is a depression in the bone into which the ball of the thumb fits, having a firm base. A little posterior to this, just above the ear, a sharp prominent mass is felt just under the skin, about the size of a pea. On stripping back the scalp, which is of normal thickness throughout, this mass is found to be a flattened bullet, approximately .22 caliber, firmly lodged in the skull cap, its entrance point lying in the temporo-parietal suture line just above the ear. The depressed area felt on external examination is found to be a perforation in the bone in the neighborhood of pterion, 1.8 cm. in size, the base formed of tough fibrous tissue which when raised exposes the brain to view. Except for a slight blackening of the tissue immediately surrounding these two regions, the scalp is of normal appearance. *Calvarium,* except as noted above, is normal; on removal it is seen that the bullet does not penetrate the inner table. *Dura* is adherent to edges of perforation; elsewhere not abnormal except that it appears everywhere so thin that the convolutions of the brain are easily visible through it. *Pia* generally normal. There is, however, very slight injection over the fossa Sylvii directly under the perforation in the skull, and a few adhesions to the dura at this point. In the process of extracting the brain a large abscess in the left lobe of the cerebellum is exposed. This abscess occupies nearly one half of the lobe in its posterior portion and contains thick, creamy, foul-smelling, puriform material. On further examination, several more similar areas are found as follows: (1) An abscess the size of an English walnut occupying parts of the second and third temporal gyri in the left. Smear from this was similar to that from the cerebellum. (2) A small softened area occupying the tip of the occipital lobe in the region of the gyrus lingualis. On section pus exudes apparently from just under the cortical gray. (3) A similar area on the other side in almost homologous position. (4) A diffusely softened area over one parietal region.

Convolutions are of normal size and in unaltered regions the cortex appears of normal depth. Fluid from the third ventricle is not purulent.[1] On the surface of the convolutions, directly below the point at which the bullet was found, appear three small brownish areas, slightly depressed, none of them more than 5 mm. in diameter; the center of each is dark brown, the color shading off toward the periphery. On the upper and posterior portion of the right mid-frontal gyrus there is a small dull white patch, 2 mm. in diameter, possibly a little firmer than the surrounding tissue, which has a slight brownish discoloration. No similar masses seen at base of brain. Except for the localized softenings described, the brain is of normal firmness, standing up well from the table. *Vessels* at base normal.

Pituitary gland. — A small, firm, white mass appears about 2 mm. in diameter. *Base of skull* normal. *Middle ears* show no signs of acute or chronic inflammation. The larger *sinuses* opened in situ contain fluid blood and post-mortem clots.

III.

A smear from the cerebellar abscess showed polynuclear leucocytes together with many organisms, some of which stained by Gram and some were Gram-negative. No tubercle bacilli could be demonstrated. Two guinea-pigs inoculated subcutaneously with pus from cerebellar and temporal abscesses respectively failed to develop tuberculosis.

Agar plate cultures were made from heart's blood and temporal brain abscess. The heart's blood culture developed one small colony, followed by two more after several days, of a Gram-positive bacillus occurring in chains. This organism was not further studied.

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[1] Cerebrospinal fluid from ventricle shows 795 cells to 100 fields. Lymphocytes, 25%; endothelial cells, 70%; plasma cells, 3%; polymorphonuclear cells, 2%.

Two plates from the temporal lobe abscess developed, one several, and the other numerous, small white colonies of a Gram-negative diplococcus.

This diplococcus grew feebly and, after seventy-two hours, practically not at all. It grew slightly on gelatine without liquefaction. Milk was unaltered by this organism. There was a slight gas production on glucose agar. There was slight stringy growth at the bottom of the bouillon tube in twenty-four hours. On blood agar the organism grew in larger opalescent moist colonies.

These organisms were not quite pure since one colony in the first plate and two in the second turned yellow and proved to consist of staphylococci. These organisms failed to liquefy gelatine.

The Gram-negative diplococcus was thought to be of more importance on account of the appearances in smear. Orbital inoculations were made in two guinea-pigs with the organism growth in bouillon, but the meninges gave no sign of lesion.

It seems probable that this organism belongs in a group related with the meningococcus, with which it corresponds in most particulars. But the peculiar abscess-production in several organs, which we are inclined to attribute to it, may serve to throw doubt on its meningococcal character. It is possible that the organism is a secondary invader in lesions produced in some other way.

We are inclined, however, to identify this organism with the *micrococcus catarrhalis.*

The *micrococcus catarrhalis* was cultivated, first probably by Kirchner,[2] in 1890, but cultivated and first named by R. Pfeiffer (oral communication to Frosch and Kolle [3]). Pfeiffer regards the organism as nearly related to the staphylocci, but as distinguishable therefrom as Gram-negative and as non-liquefying with gelatine.

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[2] Kirchner: Bacteriologische Untersuchungen über Influenza. Zeitschr. für Hyg., 1890, Bd. 9, S . 528.

In practise the *micrococcus catarrhalis* has proved to be harder to distinguish from the meningococcus and the gonococcus, sharing with them the Gram-negative staining and the frequent intracellular occurrence, as well as numerous other characters. Ghon and H. Pfeiffer, 1902, working in Weichselbaum's laboratory,[4] insist that, though the three organisms form a separate group among micrococci, they nevertheless belong to three separate species. The *M. catarrhalis* is the least pathogenic in man, and, under saprophytic conditions, grows more profusely and exhibits more vitality than the meningococcus or the gonococcus.

As a matter of diagnosis, the cultural growth of the gonococcus is distinctive enough. The meningococcus colonies are said by Ghon and Pfeiffer to be a little moister and grayer, more finely granular, as well as always less profuse than catarrhalis colonies. The catarrhalis still grows at temperature less than 20° C. The larger size of individual cocci of the catarrhalis species is said to form anothe constant feature as against micrococci.

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[3] Frosch und Kolle: Mikrokokkus catarrhalis (Kokkus bei infektiöser Bronchitis). Flügge's Mikro-organismen, 2896, Bd. 2, S. 154.

[4] Ghon und H. Pfeiffer: Der Mikrococcus catarrhalis (R. Pfeiffer) als Krankheitserreger. Zeitschr. für klin. med., 1902, Bd. 44, S. 262.

The localization of the *M. catarrhalis* in man is usually respiratory. The most frequent association is probably that with bronchopneumonia in children. Ghon and Pfeiffer found it 81 times in 132 cases of lung disease. In one case they found this organism alone, in 5 others in highly predominant numbers. Petruschky [5] found the organism in a case of typhoid fever associated with B. typhosus in the spleen, but in pure culture in the liver, kidney, and heart's blood. Weichselbaum [6] reckons this organism as of some importance in bronchopneumonia, but probably as an associated organism.

We have not yet found special statements concerning the association of *M. catarrhalis* with bronchiectatic lung conditions.

IV. HISTOLOGY.

The microscopic examination of the organs of the trunk gave the following results:

Heart not remarkable. Coronary branches thickened.

Lung. — It is difficult to demonstrate satisfactorily the bronchiectatic origin of the abscesses, since the bronchial mucosa has been largely destroyed in the process of abscess-formation. This is especially true in blocks from the central and posterior portion of the lung, where the diagnosis seemed grossly most assured.

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[5] Petruschky: Krankheitserreger und Krankheitsbild. Zeitschr. für Hyg., 1901, Bd. 36, S. 154.

[6] Weichselbaum: Diplococcus pneumoniæ und andere bei entzündlichen Lungenaffektionen gefunden Bakterien. Kolle u. Wassermann, Pathogene Mikro-organismen, 1903, Bd. 3, S. 234.

Recent purulent processes are also found throughout, with extensive masses of bacteria, both cocci and bacilli. The largest masses are coccal.

In places acute pleuritis.

Spleen. — The abscess is walled by leucocytes only, imbedded in a rather coarse fibrin. Extraordinary numbers of delicate bacilli occur within the abscess and have multiplied largely outside the leucocyte bodies. Outside the abscess wall are numerous deeply staining fragments suggesting bacteria, and among these a few characteristic slender bacilli. Polynuclear leucocytes are rare outside the abscess. Numerous plasma cells are found throughout the pulp. The Malpighian bodies are only slightly active.

Liver. — Slight periportal cellular cirrhosis. The fatty change is moderate and largely remote from portal spaces.

Pancreas. Slight chronic interstitial process.

Kidney. — The abscesses here are recent and with well-defined reaction of surrounding fixed tissues. In cells and between cells in the interior of the abscess are great numbers of minute organisms in pairs, resembling those of the brain abscesses.

Adrenal. — In the fat tissue around one adrenal there is considerable hemorrhage. Among the blood corpuscles are numerous bacteria. Several large colonies of bacteria with greenish pigment masses included are found in one place.

Cerebral cortex. — The suspicious findings in the cerebrospinal fluid led to an unusually careful search for cortical cell-pictures characteristic of general paresis of the insane.

The result of this search shows that the cerebral cortex of this case is certainly not normal, but that the pictures are far removed from those seen in general paresis.

The cortex is abnormal in several respects. Besides the coarse abscesses mentioned in the gross description, and some smaller ones found on microscopic examination, there is a certain degree of rather active subpial gliosis and a variable reduction in the number of nerve cells in the outer layers. But focal and irregular losses of nerve cells and intracortical perivascular infiltration with mononuclear cells are conspicuous by their absence.

There is a greater degree of subpial gliosis at the sulcal bottoms than over the crowns of gyri. The cells of the layer of small pyramids and to some extent those of the layer of medium-sized pyramids have suffered atrophy in some regions along the walls of the sulci, but except in the right temporal region, in no instance was this condition found above the lips of the sulci.

The cortex of the *right temporal region* will be especially described because we can very probably date its peculiar features precisely, that is, back to February, 1903, when patient shot himself in the head four years and nine months before his death. A cross-section of the right superior temporal gyrus, opposite the point of impact of the bullet, shows a singular atrophy with maintenance of cortical depth. If this atrophy can be related with the old concussion (which seems indicated by the brown spots of limited size beneath the site of the imbedded bullet), it is interesting that the outer layers are scarcely more affected than the inner layers. The maximal cell loss is probably that of the layer of medium-sized pyramids. This layer is in places almost nerve-cell-free, but never quite so, so that a senile atrophic condition is imitated rather than an arteriosclerotic atrophy. Both the layer of small pyramids and the stellate cell layer show a considerable diffuse thinning out of cells. The larger pyramids are somewhat better maintained. There is considerable subpial and medullary gliosis.

DISCUSSION.

We have presented the case of an American youth of average capacity, a chair-maker for some six years, who became insane (depressed, paranoid, suicidal, later at times katatonic) after facial disfigurement in a Fourth of July accident at the age of twenty-five. We were tempted to a more particular study of this case because of the clear-cut features of an autopsy five years after onset (chronic and acute lung disease with abscesses, multiple abscesses of other organs including the brain), which seemed to point to bronchiectases and lung disease of ancient date.

The clinical history and the autopsy findings are so far consistent that a "psychogenic" origin for this case of (possibly) dementia precox can be safely discounted. It seems safe to conclude that the lung disease was already in process of production in the six months subsequent to the episode of facial disfigurement. It is possible that this disease antedated the facial injury and that masses of bacteria in dilated bronchi had begun to affect the patient long before frank pulmonary signs set in.

However this may be, the lung disease, whose progress was carefully followed on account of its clinical resemblance to pulmonary tuberculosis, had a peculiar effect upon the course of the mental symptoms. Both lung disease and mental disease came in attacks, but these attacks did not coincide in time.

The lung disease would affect in each attack a fresh area and was characterized by exhaustion, bloody and purulent expectoration (no tubercle bacilli) and high fever.

During the toxemic phases of the lung disease the patient was quiet, but would yield depressive delusions on questioning. Just as earlier the patient had been depressed ostensibly on account of his disfigurement, so throughout his disease he tended to delusions concerning his somatic condition. ("This is leprosy I am spitting up.") But his delusions were at all times of wider range than his bodily disease ("given up by God," "world is degenerating," "murdering the whole world"), and were sometimes of extreme metaphysical ingenuity ("passed both ends of the world and got behind everybody").

After some years the paranoid picture had become emphasized by mild and episodic katatonic features (wild beast simulations, mannerisms and peculiar contortions).

It is, of course, possible that the lung disease and the mental disease are merely interpenetrating entities in this case. The autopsy showed that the brain, in common with the kidneys and the spleen and other structures, had undergone abscess-formation. There is, however, no evidence that the brain abscesses were of long standing, and, though the fatal issue was pyemic, it is probable that previous attacks had been merely toxemic, or at most mildly septicemic. The micro-organism engaged in the abscess-formation is not in all respects well-defined, but seems to belong to the *micrococcus catarrhalis* group. There is no convincing evidence that this organism was in any way responsible for the clinical features of the disease as a whole. But it seems not easy to exclude, in a more general way, the presumably highly toxic masses of bacteria and detritus in the pulmonary tissues from the field of factors in the mental disease.

Just as it has long been suspected by some workers that there is a somewhat close relation between lung disease and brain disease (and, in particular, between bronchiectases and brain abscesses), so there may possibly obtain a more delicate and elusive connection between toxic lung conditions and brain conditions. It would be of extreme value could we learn more precisely the paths taken by bacteria and toxins from the lungs to the central nervous axis.

XIX

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OBSERVATIONS ON A CASE OF PROTRACTED CEREBROSPINAL SYPHILIS WITH STRIKING INTERMITTENCY OF SYMPTOMS: ATTEMPT AT CORRELATION WITH ASCENDING MENINGOMYELITIS, CRANIAL NEURITIS, SUBCORTICAL ENCEPHALITIS, AND FOCAL ENCEPHALOMALACIA FOUND AT AUTOPSY[1]

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We have been led to attempt an unusually elaborate correlation of anatomical and clinical findings in the present case of cerebrospinal syphilis, the whole course of which lasted nineteen years, the patient being under observation of one or another physician off and on for sixteen years. The modern methods of neuropathological technique have permitted the supplementing of classical data concerning fatty degeneration (Marchi) and fiber tract destruction (Weigert) by new data concerning the progress and stage of sclerotic processes (neuroglia fibril methods of Weigert, Mallory, and Benda). Moreover, if we correlate the neuroglia fibril data with the results of cytological examination, especially of the exudative cell series, we can arrive at approximate accuracy in arranging the lesions we find in the order of their occurrence.

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[1] Read at a meeting of the Boston Society of Psychiatry and Neurology.

For example, in the present case, we can correlate with some assurance (1) the *spastic gait* with exaggeration of leg tendon-reflexes, in association with *pains in the back* and *hyperesthesia of skin of chest* (1901–2), with an intense acute inflammatory process resulting in complete inter-adhesion of the thoracic meninges and a condition amounting to transverse myelitis, the inflammatory process and resultant peripheral gliosis constantly more dorsal than ventral in position, and (2) sudden spells of *impairment of vision* (strabismus) and *tinnitus aurium* (1902) with focal and patchy cranial neuritis and peripheral gliosis about superficial origins of nerves.

But we are clearly not in a position to judge what may be the finer correlations between the very variable symptoms just mentioned, and given in more detail below, and the histological alterations (acute inflammatory and reparative changes, nuclear sclerosis, periradicular gliosis, intraradicular gliosis, and so on) mentioned below under the heading *cranial nerves.*

We are perhaps still less able to show what lesions are, and what are not, susceptible to antisyphilitic treatment. We are able to show, however, that even at the time of death, when most of the lesions had become stationary, there was still evidence of a relatively acute cellular exudation about the upper segments of the spinal cord; and a certain optimism in the persistent use of antisyphilitic treatment is thereby encouraged.

There is less ground for drawing correlations between the patient's mental disorder and the various lesions. It is a curious fact, however, that, contrary to the usual rule according to which the more delicate outer mechanisms of the cortex suffer first, the nervous system of this subject was persistently attacked *from below.* At a period when there existed peripheral nerve atrophies, transverse myelitis, extensive bilateral lesions of corpora striata, encephalitic foci of the cerebral white matter, and even a certain degree of injury to the lower layers of the cerebral cortex, the outer layers of the cerebral cortex remained fairly well preserved.

The clinical facts respecting the mental symptoms are, that, except for certain delusions and for a marked though intermittent irritability toward her nurses, the patient retained a fairly good mental capacity until the latest stages of the disease. She would indeed frequently surprise those around her by the coolness and clearness of her reasoning; to be sure, within rather narrow lines. Her optimism suggests, to be sure, a morbid expansiveness of emotion, and the two slight epileptiform seizures might be counted as possibly analogous to those of a dementia.

The history of the cord involvement is important in view of the fact that the atrophy of the thoracic cord can be shown histopathologically to have been due to several factors: (1) secondary degeneration of motor tracts from bilateral involvement of corpora striata; (2) secondary degeneration of tracts of exogenous origin from destruction of entering roots by severe meningitis; (3) degeneration of tracts at the periphery of cord as an immediate outcome of the meningitis. The only fibers preserved in the lower cord are the short fibers in the immediate neighborhood of the gray matter. Histopathologically, the peripheral sclerosis following the meningitis is of chief interest. The extensive lesions elsewhere are assignable to (*a*) plugging of arteries, (*b*) secondary degenerations following destructive lesions, (*c*) effects of meningitis. The organs of the trunk showed numerous lesions of vascular origin.

The histological work had been done with general and special methods, notably with the methods of Mallory for neuroglia and connective tissue and with Weigert's myelin sheath method.

The lesions of the cerebellum in this case have been described more particularly by Southard.[2]

CLINICAL HISTORY (J. J. P.)

This patient was first seen by Dr. Putnam in June, 1898, at which period she was 32 years old. She had been married in 1885; was without children and gave no history of miscarriages. The husband was tabetic and admitted syphilis. In 1889 the patient had had iritis, paresis of the left eye-muscles and ulceration of the throat with destruction of the uvula, for which she had been treated at different periods by Drs. H. H. A. Beach, J. O. Green, S. W. Langmaid, and Hasket Derby, all of whom had recognized the nature of her disease and had given her the appropriate treatment. Unfortunately this treatment had not been pushed to the curative point, partly because the patient had never remained steadily under the care of any one physician.

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[2] Southard, E. E. "The Neuroglia Framework of the Cerebellum in Cases of Marginal Sclerosis," Journal Medical Research, August, 1905.

The clinical record may be summarized as follows: The patient was the only child of parents both of whom suffered from cerebral disease with mental symptoms, the father having died of what was called softening of the brain, the mother having been in a private hospital for the insane for a number of years before her death, with confusion and emotional depression. As a child, the patient was talented but somewhat nervous and eccentric. At one time she had an attack of hysterical dysphasia and at another time of hysterical dyspnoea. She also had, during a certain period, an obsession which induced her to kick the mopboard at regular intervals. For many years before Dr. Putnam's attendance she had suffered from migraine of a severe and somewhat unusual type, and this is noteworthy because the migrainoid tendency seemed to mix itself in with the symptoms due to actual brain lesion and degeneration. The minutes made on June 10, 1898 say: "The patient had a very severe attack of migraine (?) yesterday, preceded and accompanied by paraphasia, so severe that for three hours she was unable to make herself understood and indeed felt 'as if her ideas were getting away from her.' This attack was ushered in by a numbness of the forefinger and thumb of the right hand which lasted for about three hours though the earlier attacks had usually lasted only for about ten minutes. During this period the hand felt as if it had been frozen and the loss of muscular power was so great that she was unable to hold objects in the hand. In some of the attacks this paræsthesia has affected the entire left half of the body and occasionally the right half. Sometimes the seizures come on with great suddenness, so that once, when she was attacked while in the middle of the street, she had considerable difficulty in reaching the sidewalk. After the worst part of the attack is over a certain amount of paraphasia may persist for some days, together with awkwardness in the use of the right hand and numbness. She has had a great deal of nausea and vomiting, without reference to the taking of food."

The physical examination showed a systolic murmur at the apex and base of the heart, which, however, was obviously of functional character, and passed away later. The second aortic sound was somewhat accentuated. The left pupil was larger than the right but both reacted well to light. The urine was analyzed and found to be substantially normal. The patient at that time was put on a course of potassium iodide, in increasing doses, and biniodide of mercury.

The patient then passed out of Dr. Putnam's hands, and he did not see her again until May, 1902, when she was referred to him again by Dr. C. F. Folsom, who had been recently called to examine her. She was still subject to the migrainoid attacks, but it was found that, in addition, serious symptoms of a transverse myelitis had set in (during the summer of 1901), preceded by severe pains in the back, the significance of which had not at first been recognized. Her gait had become very spastic, so much so that she could not walk alone, and the tendon reflexes of the legs were all very much exaggerated, especially those upon the left side. The leg and foot muscles were seized from time to time with severe and prolonged cramps. There was incontinence of the urine and to a great extent of the feces. Cystitis was also present. One very distressing symptom of especial interest was a hyperæsthesia of the skin over the chest, especially on the left side, and this was so severe that the contact of her clothing caused her great annoyance. She had had recently two or three slight epileptiform seizures without complete loss of consciousness, each lasting about five to eight minutes. Her mental condition was slightly disturbed to the extent that she was very irritable and excitable and a little violent, occasionally striking out petulantly at her nurse. Although she ate a large amount of food she had a species of delusion that she was suffering from loss of appetite. Her sleep would have been good except for the involuntary micturition. In August of the same year she began to have attacks of impairment of vision (probably due to slight strabismus) coming on suddenly and at short intervals, and with these there was sometimes sudden loss of hearing of similar duration, with ringing in the ears. Sometimes twenty such attacks would occur in one day, each lasting three or four minutes.

Under large doses of potassium iodide and mercurial inunction all these symptoms were considerably relieved, the change being especially striking with relation to the hyperæsthesia of the chest, which disappeared altogether for a considerable period.

The treatment was pushed from time to time to the limit of endurance, although it was necessarily interrupted occasionally on account of increased micturition due to the iodide, and of a threatening of salivation.

During the next year she did fairly well, but sometimes suffered from new symptoms or an exacerbation of old ones. Thus she thought herself watched and became suspicious of those around her; when she went out to drive she was possessed with the idea that absent relatives were waiting for her at home; at times she would have attacks of hysterical laughter, especially when attempting to walk. In spite of early improvement the difficulty in locomotion began after a time to gain ground, and in the course of 1904 she became practically confined to her chair. A blurring of vision due to paresis of the muscles of the eyes, especially of the left, made its appearance occasionally, then yielded to treatment, but finally reached a point when it would no longer yield.

The variability of certain symptoms, partly but not wholly to be explained as the effect of the treatment, was in some respects very remarkable. Thus, in the course of 1904 her hearing became rapidly impaired so that at last she was absolutely deaf and no communication by the voice was possible; yet some months before her death (1905) she improved for a short time rapidly and remarkably in this respect, although in other respects emaciated and suffering from the infection of huge bedsores. Finally the hearing was again, and this time permanently, lost.

In similar fashion, the knee-jerks, which had been exceedingly exaggerated, disappeared about November, 1904, but again returned for a brief period a short time before her death.

From November, 1904, she was completely paraplegic and at about the same date, or somewhat earlier, the movements of her hands and arms, which until then had remained free, began to suffer. Her mental condition deteriorated steadily throughout the last year, but she still clung, as if with the tenacity of obsession, to the belief which she had entertained throughout, that in the end she would get well, and when hardly more than a ray of intelligence seemed left she still showed a childish delight at the gift from her husband of a valuable ring which she had long desired.

Several months before her death bed-sores made their appearance on the sacrum and on the feet, and in spite of the most vigilant care increased to an enormous depth. These sores gave rise to infection, and to fever of a septic character, in spite of which she showed the tenacity of life characteristic of the long-time invalid, dying finally on February 7, 1905, after lying practically unconscious for several days.

Summary of Clinical Findings

A woman of 23 acquired syphilis in 1889. In 1894 she began to suffer in an exaggerated form from a constitutional tendency to severe headaches, resembling migraine and accompanied by attacks of paræsthesia. In 1901 the patient began to have severe pains in the back and difficulty in walking. In 1902 the migraine was accompanied by blurring and dizziness, the difficulty in walking became extreme, affecting particularly the right foot, and the legs became spastic. There were pains and hyperæsthesia of the chest and severe cramps of the legs. These symptoms improved under antisyphilitic treatment. In the middle of 1902 came transient losses of vision and of hearing besides irritability and delusions about her relatives and a few epileptiform seizures. In 1904 total deafness; improvement later. Variable involvement of the eye muscles with intervening improvement. Loss of knee jerks; later partial return. In November, 1904, absolute paralysis and extensive decubitus. Death in 1905, at the age of 39, four years after the onset of the myelitis, eleven years after onset of earliest nerve symptoms, sixteen years after acquiring syphilis.

GROSS FINDINGS AT AUTOPSY (E. E. S.)

Slender woman of middle height. Extensive sacral decubitus. Open ulcers of inner surface of feet. Skin of abdomen shows numerous dark brown macules, varying in diameter from .5 to 1 cm. Traces of mercurial inunction over breasts. Pupils wide; left pupil 8 mm., slightly irregular. Hair black.

Trunk.—Abdominal fat 1.5 cm. deep. Peritoneal, pleural, and pericardial cavities normal. Heart: Weight 190 grams. Epicardial fat slight. Muscle slightly opaque-yellow. Endocardium and valves normal, except for a slight thickening of mitral valve edge without notable shortening of chordæ tendinæ. Coronary arteries normal. Lungs: Apices slightly puckered over minute firm brown and black pigmented areas. Similar brownish pigmented area, at upper border of middle lobe of right lung, externally suggesting infarct, on section brownish and in places gelatinous. Pulmonary arteries show faint traces of sclerosis. Bronchi contain frothy fluid. Bronchial lymph nodes small and black. Spleen: Small, firm, only slightly pulpy, with markings distinct. Liver: Almost one-third enlarged, with rounded border, fatty. Gall Bladder: Normal. Gastrointestinal Tract: Externally normal. Pancreas: Normal. Kidneys: *Left* reduced to a pouched sac, from .25–.5 cm., thick, filled with foul smelling fluid and communicating with a dilated ureter which gradually loses in calibre till it opens in a slightly pouting papilla. A probe readily passed from bladder into ureter. *Right* kidney large. Markings distinct. Cortex shows a diffuse slightly opaque yellow color, more marked in radii corresponding with tubule systems. Right ureter of normal size and appearance. Adrenals: Normal in gross (but v. microscopic examination). Bladder: Firmly contracted. Wall very thick at fundus. Genitalia: Externally normal.

Head.—Scalp normal. Calvarium: Heavy and with little diploë. Dura adherent to parietal bone. Arachnoidal villi: well developed. Inner surface of dura moist with a slightly stringy fluid containing a few fibrin threads. There are a few adhesions between dura and pia over central convolutions external to the zone of arachnoidal villi. Pia shows clouding over sulcal veins, notably over vertex and along Sylvian fossæ, and diffuse thickening over tops of gyri in vertex region and over superior vermis, besides several foci in both hemispheres of cerebellum. Pia peels readily but the small vessels are a little stiffer than normal. Optic nerves bound to base of brain by a thin but dense sheet of fibrous tissue. Wall of cisterna slightly thickened. Pia over pons and medulla notably thickened.

Cranial Nerves.—Olfactory nerves normal. Optic nerves of the usual diameter with a thin translucent outer zone. Left third nerve normal: right third nerve about one-third the diameter of the left. Fourth nerves equal and apparently normal. Sensory portion of left fifth nerve thinned out; right fifth nerve normal. Left sixth nerve normal; right sixth nerve reduced to a thread at a point 2 mm. from superficial origin. Left seventh and eighth nerves thinned out. Right seventh and eight nerves normal. No macroscopic changes in the other cranial nerves.

Vessels.—Right vertebral artery reduced to a thread. Left vertebral artery small, upon incision shows a longitudinal raised line of sclerosis. Carotid arteries slightly stiff. No other gross evidence of sclerosis.

Substance.—Fairly firm. Convolutions suggest a slight general narrowing of the cortex, but this has produced a demonstrable flaring in a few areas only, notably just behind the posterior central convolution of the left side, about 6 cm. from longitudinal fissure. There are numerous small, ill-defined areas of hyperemia and slight swelling in the cortical gray matter, of irregular distribution and a few millimeters or centimeters in diameter. These areas are very faintly visible from without. No vascular lesions are demonstrable in connection with the focal lesions. Centrum semiovale normal. Fibers of forceps minor and tapetum cut with difficulty.

Ventricles.—One-third dilated. Ependyma of floor of bodies of both lateral ventricles shows a brownish discoloration, corresponding with the extent of the caudate nuclei. Ependyma elsewhere normal, except over the floor of the fourth ventricle which shows a fairly marked sanded appearance.

Basal Ganglia.—Show on section roughly symmetrical destructive lesions of the corpora striata: (1) The intraventricular portion of the caudate nucleus is on both sides reduced to a lamina 1–2 mm. thick corresponding with the discoloration of ventricle floor. (2) The anterior segment of the internal capsule is on both sides reduced to a densely cutting lamina with the fiber bundles somewhat more widely separate than normal. The anterior segment on the right side is more markedly affected and is almost bisected by a cystic cleft running up from the lenticular nucleus below. (3) Both lenticular nuclei are largely replaced by a grayish tissue, in places discolored but nowhere injected and retracting under the knife to give the appearance of ill-defined cystic clefts containing a semi-gelatinous cloudy fluid.

No other focal lesions occur except in the cerebellum. Marginal convolutions of cerebellum show thinning of cortical substance, best marked near superior vermis and along posterior notch. The outer portion of the amygdala and inner portion of the biventral lobule on the left side show a destructive lesion with depression 1.5 cm. in diameter by .5–7.5 cm. in depth. The depression is lined by brownish moist pia mater, dipping gradually down from the surrounding marginal convolutions, which show a well marked cortical atrophy. The lesion on section shows effacement of normal markings and a smoothly cutting jelly-like brown substance, here and there yellowed and slightly opaque.

Spinal Cord.—Dura thicker than normal, notably along thoracic cord. Arachnoid space contains numerous fibrous adhesions and is quite obliterated in the thoracic region. The cord on section is considerably, perhaps one-fourth to one-third, reduced in diameter, notably in thoracic and lumbar portions. The outer border of the cord is everywhere abnormally translucent for a distance of .2–.3 mm. The pyramidal tracts, the direct cerebellar and anterolateral tracts, and the upper and outer portions of the tracts of Burdach show symmetrical gray degeneration throughout the cord. The tracts of Goll vary, although symmetrically, in the amount of gray degeneration shown; in places there is a considerable triangular white column in this region with its base applied to the gray commissure. The only white matter regularly preserved throughout is the ventral field of the posterior columns and the anterolateral ground bundle; the processus reticularis is particularly prominent. In the thoracic and lumbar regions the gray matter is relatively reduced in amount. In the lumbar regions, within the gray matter, there is an occasional minute cystic cleft on section, corresponding with the anterior horn, and an occasional minute lesion (under 1 mm. in diameter) with a white center and brownish translucent border (one noted in processus reticularis in lower dorsal region). The white fibers of the anterior roots are prominent, as they pass from the lumbar anterior horns to the periphery of the cord, by reason of the gray degeneration of the whole anterolateral columns in this region. The cauda equina shows a notable thinning out.

Anatomical Diagnoses

Atrophy of cortex of cerebrum and cerebellum and of spinal cord. Chronic diffuse cerebrospinal leptomeningitis, notably of vertex, base, and in thoracic region of cord. Adhesions between dura and pia over vertex. Symmetrical destructive and atrophic lesions of gray matter of both corpora striata, with atrophy of anterior segments of internal capsules. Induration of forceps minor and tapetum. Atrophy of right third and sixth, left seventh and eighth, and sensory root of left fifth cranial nerves. Destructive lesion of amygdala and biventral lobule of left cerebellar hemisphere. Gray degeneration of long tracts in spinal cord. Destructive focal lesion in anterior horns in the lumbar region of cord. Atrophy of fibers in cauda equina. Extensive decubitus. Macular discoloration of abdomen. Irregular pupils. Small fatty heart with slight chronic mitral endocarditis. Fatty liver. Left hydronephrosis with dilatation of ureter (no cause for obstruction evident). Fatty kidney.

Microscopic Examination

Heart.—The fibers are unaltered except for the presence in a few of vacuoles containing fat. There are no demonstrable changes in framework or vessels.

Aorta.—All three coats of the ascending arch exhibit changes. The intima shows fibrous thickening in low waves, nowhere over 0.5 mm. deep. At the base of some of the intimal elevations are lighter areas with connective tissue cells and with fibrillæ; opposite such areas the media is slightly diminished in thickness. The media exhibits in the main a normal arrangement of tissues, but tends to cleave along a belt varying from one-tenth to one-third the diameter of the total zone. This belt in the media shows a loss of muscular tissue, an excess of fibrous tissue, and an apparent if not actual increase of elastic tissue. Beneath the lighter non-fibrillated areas at the base of the intima the tissues in the non-muscular belt show a few small vessels and some dislocation of elastic and fibrous bands, which run at several angles. The small vessels of the adventitia show a moderate infiltration of sheaths with cells of the lymphoid and plasma cell series.

Lung.—The air spaces are in places distended, in places collapsed, and sometimes contain collections of pigmented cells. Near the infarct the spaces contain many polynuclear leucocytes and there is purulent bronchitis. The walls of the spaces contain an excess of elastic fibers. In places there are large thrombosed and thrombosing vessels, some of them with quintuple or sextuple elastic layers. Some of the vessels are canalized.

The lymph spaces of the bronchial nodes contain numerous polynuclear leucocytes and mononuclear leucocytes not phagocytic.

Spleen.—The pulp contains much pigment, free and within cells, and a moderate number of polynuclear leucocytes. The muscularis of some small arteries shows hyaline deposit. Some of the Malpighian bodies show hyaline deposits with a few strands of connective tissue.

Liver.—Advanced fatty change with vacuoles of various size, some much larger than liver cells. Condensation of fibrous tissue in portal tissues with lymphocyte infiltration.

Pancreas.—A few vessels show an excess of fibrous tissue in the intima. Parenchyma and islands show no lesion.

Kidney.—Many vessels show a mild grade of intima proliferation. Occasional glomeruli are atrophied. There is in places a slight excess of intertubular fibrous tissue. The tubular epithelium is pale, swollen and granular. The pyramidal tubules contain many hyaline casts.

Adrenals.—Show several areas of infarction with occluded vessels.

Central Nervous System

The lesions in the central nervous system are of very manifold character and may be considered under the heads of *cerebrum* (leukencephalitic foci, perivascular cellular glioses, subpial sulcal fibrillar glioses, numerical cell-losses in stellate and substellate layers); *basal ganglia* (cysts of softening), *cerebellum* (cyst of softening), and spinal cord (severe meningitis, especially thoracic, with duro-pial adhesions; peripheral gliosis, especially over lateral columns; mild chronic exudative myelitis, especially cervical; dilated perivascular spaces in gray matter). A note is added concerning the *cranial nerves* (irregular and patchy atrophy).

Cerebrum.—The microscopic examination of the cerebral cortex served to confirm the impression gained from the gross examination that strikingly few lesions exist therein.

There was a suggestion of *encephalitic foci* in the gross. The most convincing evidence of these foci microscopically consists in certain venous plugs of polynuclear leucocytes, found both in the meninges and in the cerebral cortex. The local hyperemias noted in the gross are microscopically found to be largely due to venous congestion. The evidence of acute encephalitis is exceedingly slender. An occasional polynuclear leucocyte is found in an extravascular position.

It is less easy to explain the local swellings than the attendant hyperemia. Nevertheless, there is one interesting finding in the white matter of numerous gyri, which may throw light on the local swellings. The white matter contains numerous small rounded or globular foci which stand out, in eosin-methylene blue sections, from their pallor. This pallor is in part due to faint staining of myeline sheaths, in smaller part to absence of some myeline sheaths and consequent spreading of structures within the focus. The neuroglia nuclei are in part swollen and highly vesicular and in part collapsed and pyknotic. These foci are not of universal occurrence. They do not appear to be directly related to vessels.

It is possible that these areas represent the earliest phases of a *leukencephalitis*, such as has proceeded to a far greater degree in the spinal cord. It is just possible that these areas represent the effects of syphilotoxines. The occurrence of considerable decubitus in the case gives rise to another hypothesis, however, that of intercurrent infection. It does not seem possible to decide between these hypotheses. A middle ground may be taken if we consider that such lesions are due to intercurrent invasions of bacteria or to introduced bacterial toxines which are somehow permitted to act through antecedent or existent syphilis.

At all events it is likely that a series of such leukencephalitic processes would favor progressive degeneration of the white matter and might prove to be essential steps in the syphilitic process.

In addition to areas of venous congestion and recent leukencephalitic foci, the cerebral convolutions show a few processes of more chronic type. There is a trivial degree of *perivascular gliosis* related with the larger vessels of the white matter; this gliosis appears to be somewhat recent. Scarcely more extensive, but a trifle older in date, is a mild subpial gliosis which is of greater degree in the sulcal depths than on the surface.

The mental phenomena clinically observed render cortical conditions of considerable interest. One feature common to all the areas examined is the relative intactness of the outer cortical layers as compared with the inner layers. The fusiform cell layer has suffered numerically in many places in rather an unusual degree. The stellate and substellate layers frequently exhibit bare spots or areas poorly provided with nerve cells, recalling the minor variations in cell supply found in senile cerebral atrophy. This process in the lower layers accompanied by tolerably well preserved upper layers gives a rather unusual total impression to the cortex.

To sum up, the cerebrum microscopically confirms the impressions of the gross and shows a mild chronic degeneration, characterized by subpial sulcal fibrillar gliosis and perivascular cellular gliosis, cell-atrophy with numerical losses in the stellate and substellate layers, besides more acute and recent processes (a mild focal leukencephalitis and congestion with leucocytosis of numerous veins).

Basal Ganglia.—The lesions under the lateral ventricles are old cysts of softening. The cleft-like spaces are filled with albumin coagulum and pigmented cells and are traversed by numerous small vessels. The walls of the cysts are composed of neuroglia fibrillæ which run for the most part parallel with the cyst borders and include numerous flattened nuclei. The picture changes gradually, so that the adjacent tissue, less than 0.5 mm. distant, shows a more active set of cells in which the cell bodies are symmetrically enlarged and centrosomes are demonstrable. The overlying ependyma is in places normal and shows the usual supply of superficial dots and occasionally a good demonstration of cilia. Upon approaching the deepest portion of the cleft now representing the caudate nucleus, the ependymal nuclei gradually accumulate to form a layer several deep, the superficial dots occur in more rounded collections, and the cilia fail to appear. In places the ependymal cells no longer maintain a compact arrangement, but occur in clumps and rings at a short distance from the membrane. In the latter case the cell-aggregations somewhat resemble giant cells; among the nuclei occur rounded collections of dots which cannot be distinguished from the superficial dots of the ependymal membrane.

Cerebellum.—Cyst of Softening.[3] The focal lesion in the cerebellum is an old cyst of softening. The smoothly undulating walls are composed of densely fibrillar neuroglia. The interior consists of numerous capillaries with loose fibrous coats and surrounding spaces which contain fibrin, albumin coagulum, and great numbers of swollen cells enclosing granular pigment. Similar cells are dotted throughout the wall in small spaces, which give the tissue a sieve-like appearance on cross section. The intrinsic glia cells in the cyst wall are few and inactive. The fibrils are fine and of even diameters, although where they abut upon or make out into the cyst they may become coarse agglutinated masses.

Some of the laminæ of the cerebellum, especially the marginal gyri and the gyri around the cyst of softening, show a loss of substance which is peculiar. The contour and stratification of the affected laminæ remain, but the component tissues have undergone a differential loss of substance. The nerve elements have disappeared. The white core contains no myelinated fibers. The Purkinje cells and their appertaining dendrites are absent. The layer of small nerve cells known as granules is represented only by a layer of neuroglia cells. The remnant of the inner or granule layer, with its dense feltwork of neuroglia, serves to maintain the contour and suggests the stratification of the normal cerebellar cortex. Radiating out from the modified inner layer are bundles of coarse neuroglia fibrils which, in situation at least, recall the fibers called Bergmann's fibers. Among these fibers there occur for wide areas no cell-bodies whatever. In many cases the bundles can be demonstrated to run all the way from the pia mater, where they may spread out to imitate a foot, to the neighborhood of the cells of the granule layer, which cells the fibrillæ embrace in the characteristic fashion of neuroglia tissue. The nuclei of the cells related with these radial fibrillæ are large, oval, vesicular, and provided with numerous chromatin dots; cell-bodies are rarely visible. Similar cells stand in similar relation to numerous finer fibrillæ which run concentrically about as a kind of central beam for the granule layer. A third series of fine fibers runs at right angles to the two preceding, is derived from similar cells, and occupies the locus of the Purkinje cell layer. The tissue replacing the central core is composed of numerous fibrillæ running in many directions, together with their cells of origin and a few vessels. In some laminæ the impression is gained that fibers similar to Bergmann's fibers, or continuous with them, radiate inwards from the granule layer, but the core fibers are often so abundant as to obscure this picture.

Spinal Cord.—The cord of this case is a good field in which to demonstrate the pure effects of old meningitis as opposed to the effects of secondary degenerations, since the meningitic process varies with some regularity down the cord, whereas the secondary degenerations in the long tracts persist throughout in maximal degree.

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[3] For plates, see Southard, *loc. cit.*

The meningitic process, as might be surmised from the clinical history, is severest in the thoracic region. Here, not only is there an extensive neuroglia thickening of the subpial region, together with a thickening of the pia mater, but also the dura mater is so firmly attached to the pia mater that the line of demarcation is sometimes hard to make out.

The condensing process which has gone on in these tissues was, at the time of autopsy, well-nigh at a standstill. Scattered lymphocytes (no plasma cells) lie in the meshes of the fibrous tissue, accompanied by old pigmented cells of endothelial type. Opposite the points of greatest condensation, namely, at the most prominent points in the lateral columns, there is no longer much evidence even of lymphocytosis, and here the tissue seems wholly quiescent. The effect of this lesion must have been to cut off intercommunication between subdural spaces above and below.

Examination of the cord itself at numerous levels shows that the brunt of the meningitic process is always borne by the most prominent portions of the lateral columns. Even at levels where there is little or no interadhesion of pia and dura mater, the neuroglia tissue is found to be most strengthened over the lateral columns. It is even probable that this peripheral gliosis, which was best demonstrable by Mallory's phosphotungstic acid hematein stain, is a more delicate sign of former reaction than is the pial thickening.

It seems difficult to explain why the peripheral gliosis should take maximal effect upon the lateral columns. In the present case the crossed pyramidal tract gliosis underlying this region may have contributed to local tissue tension, and therefore have aided the glia-formation. If this were the case, however, it might seem reasonable that the tabetiform lesion of the posterior columns should serve to deepen the glia-reaction over the posterior columns. As a matter of fact the peripheral gliosis of the posterior columns stands next in depth and density to that of the lateral columns, but is rarely if ever so severe.

Taken together, however, it is certain that the posterior columns, the posterior root zones, and the lateral columns (especially in the posterior two thirds) much outstrip the more anterior parts of the cord in severity of gliosis. There is also reason to think that the toxine or other agent at work to produce this gliosis is the same which is responsible for the lymphocytosis of these regions.

Lymphocyte-infiltration amounts at some levels to a mild myelitis. The most active region in this respect at the time of death was the cervical. Here, although no marked differences can be made out in the degree or quality of gliosis, it is evident that the perivascular infiltration prefers the above-mentioned regions of maximal gliosis and especially the posterior root zones. It is evident that this distribution of lesions would favor the occurrence of disorders of sensation and very probably the priority of these in the clinical history.

The signs of frank myelitis, aside from the gliotic reactions to destruction of long tracts and to meningitis, are few. The later clinical history had pointed to alterations of the state of the anterior horns. The gross examination of the cord at autopsy so far bore out this suspicion that minute cystic clefts and certain small whitish spots with brown borders were found in the anterior horns of the lumbar region. The small cystic clefts were rediscovered in microscopic section and proved to be of the banal type of dilated perivascular spaces, with which one is so familiar in the tissues of general paretics and of other organic cases. Into a few of these clefts there had been a slight extravasation of blood. No lesions corresponding with the above-mentioned white spots were found in the numerous segments studied; it is possible that they corresponded with local variations in gliosis combined with the results of minute hemorrhages.

At all events there is little evidence of frankly destructive myelitis of a focal character throughout the cord.

The manifold secondary degenerations in the cord require no further or special mention.

Cranial Nerves.—The clinical history, it will be remembered, showed sensory and motor disorders which varied markedly in their extent and were in some cases apparently cured only to recur once more; in some instances this alternation was repeated.

It seems *a priori* unlikely that such disorders can be due to focal losses of the type due to blockage of vessels. In case a given nerve is directly in an area of infarction, it seems unlikely that a repetition of symptoms would be brought about by a second process of infarction affecting the same nerve.

Far more likely is such a series of symptoms to be due to a meningitic process of possibly varying severity. Not only may the peripheral nerve involvement vary in severity in proportion to the intensity of meningitis about the superficial origins, but, in such a case as the present, the factor of peripheral subpial gliosis becomes of extreme importance. Moreover, in the case of certain nerves, like the optic and the seventh and eighth, neuroglia may overgrow within the nerves themselves and add to the possibilities of functional impairment.

From purely general considerations, therefore, it develops that in a case of basal meningitis an extensive series of factors can be responsible for functional disorder, viz.: (1) The edema and cellular exudation of an acute pial inflammation; (2) The contraction of the pial tissues in repair after inflammation; (3) The local acute neuroglia reaction (cellular gliosis) involving roots at the superficial origins; (4) The contraction of neuroglia tissue (fibrillar gliosis) about the emerging roots; (5) and (6) Acute and chronic gliosis within certain nerve roots themselves. (7) In addition to these factors, a case like the present, with extensive atrophy of interior tracts, may in the process of general contraction of the parts and the corset-like effect of advancing chronic meningitis, exhibit a curious herniation outward of nerve tissues through points of weakness in the surrounding pial tissues. The type of hernial gliosis due to compression from without is seen at its best in the compressed spinal cord, especially in a case like the present with extensive duro-pial adhesions.

It would be advisable to study these conditions in greater detail in a series of cases; but enough has been said to show that the histologist possesses a considerable gamut of reactive processes with which to explain a series of functional impairments in the same region.

It is naturally not easy at autopsy in a given case to assign dates to the different lesions shown. The hypothesis remains open always that a part of the phenomena were of a hysteroid nature superimposed upon the results of focal tissue losses.

Of especial interest in this case is the occurrence of factors (5) and (6) (of the above enumeration) in the cranial nerves of this case. Gliosis in the nerve origins may possibly account for the extreme irregularity of the atrophies observed (right third and sixth, left seventh and eighth, sensory root of left fifth). That these atrophies are in part of central or even nuclear origin cannot be denied. But the *focal and patchy character* of the lesions within the affected nerves themselves gives every hint of a local origin for a part of the phenomena.

The left eighth nerve was, on account of its size, especially studied in neuroglia preparations and shows a unilateral area of rather sharply marked fibrillar gliosis, recalling in some respects the appearance of an area of multiple sclerosis. But no appearances suggesting axis-cylinders can be made out in the area. In addition to this focus there is evidence of an exudative perineuritis (lymphocytosis).

REMARKS

It is interesting in the light of the above history and findings to consider what clinical moral is to be drawn for further guidance. It is obvious that amongst the many sorts of lesions that were present some remained susceptible of influence by treatment to the last, while others went slowly on their way.

In general terms, it might be said that most of the fresh symptoms, unless perhaps those of mental character, passed away, for a time at least, under large doses of mercury and the iodides, and the histological investigation shows the reason for this favorable response. The question arises whether under the still more constant use of these remedies a wider and more permanent improvement would have been secured. It is quite possible that this would have been the case or that at any rate the occurrence of fresh outbreaks would have been forestalled and possibly prevented. Nevertheless, there seems to come a time when the power of mercury and iodides to secure benefits reaches its termination. To say the least, it is probable that there are some cases where it is impossible to bring about a complete immunity form further action of the syphilitic poison and it is obviously impossible to prevent the gradual impairment of the nutrition of the central nervous system through the formation of cicatrices and secondary degenerations. Nevertheless, in another case we should use these remedies at shorter intervals and if possible in larger doses.

A case observed by one of us during the past few years has lent special significance to this view. The patient. a man of middle age, was almost paralyzed from the neck down, when first seen in consultation, suffering from dyspnea and paresis of all four extremities, especially the legs, with highly exaggerated reflexes; all due, as the autopsy eventually showed, to lesions of the upper cervical cord. Under very large doses of potassium iodide, amounting finally to eight hundred grains a day, combined also with mercury, improvement set in and practical recovery followed. The treatment was continued for a long time but eventually was omitted. At the end of about a year or two of relatively good health, unfavorable signs of renewed outbreak in the same region again showed themselves, and the patient not then being under close observation did not at first receive adequate attention. When he was seen treatment was resumed and pushed, but he grew rapidly worse and died.

The autopsy showed a fresh gummatous formation in the cervical region of a kind that at an earlier period would probably have yielded rapidly to treatment. But in these late cases treatment, to be effective, has to be more vigorous than at earlier periods.

It is difficult to say whether certain of the improvements,—especially that in walking, when in 1902 vigorous treatment was again resumed, but when likewise systematic training of the muscles was undertaken—were due to the anti-syphilitic treatment or to functional stimulation. It is likewise difficult to say whether the patient was suffering from a constitutional tendency to cerebral degeneration to which a portion of the mental symptoms might justly be referred and whether the extraordinary migranoid attacks, which grew more protracted and more complex until the last year of the patient's life, had a portion of their origin in the lesions of syphilitic origin. It is notable that in the cases of patients liable to migraine, who suffer later from intra-cranial new growth, the headache due to the latter cause seems to be colored by the constitutional tendency, and a similar mixture of causal influences may have been present in this case. Certain it is that the hysterical tendencies of the patient made it very difficult for the physician to judge as to the exact character of the enemy with which he had to deal.

Perhaps the most important moral of all is that the time when the vigorous and prolonged anti-syphilitic treatment might have really killed the snake instead of only scotching it, was during the earlier portion of the illness, and that the temptation to regard the healing of ulcerations and the disappearance of acute symptoms as an indication for ceasing vigorous treatment is one that cannot too strongly be resisted.

One of the writers has recently seen a case of syphilitic meningo-myelitis which at first had been imperfectly treated, improve rapidly under more vigorous treatment, only to give place finally to a mild tabes, a result which a still more vigorous early treatment might possibly have obviated.

CONCLUSIONS

The very varied problems and considerations of this case may be set forth as follows:

1. A protracted case of cerebrospinal syphilis shows at the end of sixteen years after infection and eleven years after initial nerve symptoms, a multiplicity of chronic lesions, but shows few acute lesions save (*a*) lymphocytic exudation in the upper spinal cord segments (preferring the posterior root regions) and (*b*) certain interesting leukencephilitic foci in the brain. Possibly both (*a*) and (*b*) are related to intercurrent

infection from extensive decubitus; this is more likely in the case of (*b*). Search for spirochetæ so far negative.

2. On the basis of gross and histological findings, it is possible to correlate many of the various clinical features: (*a*) transerse myelitis, (*b*) intermittent cranial nerve and other symptoms, with structural disorder. But there were hysterical tendencies throughout which rendered exact correlations difficult *intra vitam.*

3. The intermittency of symptoms just mentioned (2 (*b*)) was most striking, and an enumeration of histological possibilities is given which might account for this intermittency (acute and reparative changes in the pia mater; cellular and fibrillar gliosis whether nuclear, periradicular, or, in some cases, intra-radicular; and the corset-like contraction of whole regions subject to sclerosis, with consequent herniation of small bits of nerve tissue).

4. The intermittency and varied structural origin of the symptoms, as well as the maintenance to the last of acute changes mentioned under (1) are reasons for optimism in pushing anti-syphilitic treatment.

5. Incidentally, the post-mortem data show how lumbar puncture might fail to reveal lymphocytes in cerebrospinal syphilis, provided that there is an occlusion of the intermeningeal space by adhesions above the point of puncture.

6. The case presented a kind of reversal of the biological tendency that the structures later evolved shall be destroyed first, since the course of lesions in this case was largely ascending throughout and the cerebral cortex was left at the last a species of shell from which the lower functioning mechanisms had been successively scooped out by disease.

XX

NEUROPHYSIOLOGICAL EFFECTS OF ANAPHYLACTIC INTOXICATION.*

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The main physiological facts of anaphylaxis,[1] particularly of horse serum anaphylaxis in the guinea-pig,[2, 3, 4] are sufficiently established. Progress now leads in two separate directions, the one practical, the other theoretical.[5] The most important clinical applications of our knowledge of anaphylaxis are, first, a caution as to the use of horse serum mixtures (such as diphtheria antitoxin) in asthmatics,[6] a point now established by manifold clinical experiences,[7] and, secondly, the application of the phenomenon of "transferred anaphylaxis," described by two of the writers in their first communication,[8] in the diagnosis of tuberculosis (Yamanouchi)[9] and typhoid fever (Ascoli).[10] Important as anaphylaxis may prove in relation to bacterial infections[11] and suggestive as are certain other claims as to the importance of anaphylaxis in heredity[12] and in diseases having recurrent crises,[13, 14] it does not appear that practical progress will attain its maximum until a sufficient theory shall supplant the numerous hypotheses now in the literature.[15]

We have, therefore, persisted in work along theoretical lines, regarding horse serum anaphylaxis in the guinea-pig as the field containing the most facts at the present time. The possibilities of theoretical progress in anaphylaxis lie also in two directions, in the direction of histopathology and in that of physiology. On the histopathological side we regret that few workers have shown proper interest, nor have the observations of Gay and Southard been adequately repeated by other workers.[16] The histopathological work so far done, as well as several of the hypotheses in the literature, indicates that the nervous system is to be the most fruitful field

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of investigation. Accordingly, in the present communication, we wish to bring out certain physiological evidence which will indicate the best histological point of attack.

In 1908 two of the writers adduced evidence as to the cause of death in serum intoxication[17] and mentioned certain hypotheses in the literature. The "latent brain lesion" hypothesis of Besredka[18] contains little more specific than that Besredka considers that horse serum acts upon a specially sensitized brain. Rosenau and Anderson are committed (as well as Vaughan and Wheeler in the analogous field of egg-white[19]) to the hypothesis of specific toxic action upon the respiratory centers. With respect to these hypotheses, we have shown that organs other than the nervous system are involved in the process of anaphylaxis and that parts of the nervous system other than the respiratory center exhibit effects in the critical phase.

We have undertaken experiments to show in greater detail than in 1908 the differential effects of injections, both near (paraneuraxial) and in (intracerebral, intracerebellar, intrabulbar) the central nervous system, as well as certain peripheral nerve experiments.

PARANEURAXIAL INJECTIONS. — Injections of horse serum in the fluid spaces about the central nervous system (paraneuraxial injections) in sensitized guinea-pigs cause a variety of symptoms according to the locus chosen.

The amount necessary to produce symptoms or death by paraneuraxial injections is small, probably as small as the amount necessary by the carotid artery or the jugular vein. We have used doses of 1/20 cubic centimeter in the majority of our experiments.

Proximity to the respiratory centers seems to govern the rapidity and to some extent the violence of the symptoms.

Experiment 1. Cervical spinal cord. — Guinea-pig S_I (sensitized March 4, 1908, by intraperitoneal injection of five cubic centimeters horse serum). April 7, at 3.49 P.M., .75 cubic centimeter horse serum was injected into the tissues adjacent to the cervical spinal cord. At 3.51, rapid respiration, which increased and at 3.59 was ninety-eight per minute and irregular. The respirations suddenly increased if the guinea-pig was disturbed by contact or movements of adjacent guinea-pigs, and later became extreme and maximal, afterward slowing down. The irritative stage was succeeded at 4.09 by a paretic stage, guinea-pig flat on belly, occasionally starting up and breathing hard. Wiping movements with left fore-paw. At 4.19, crural paraparesis, later recovery. At 4.34, restlessness with frequent sudden convulsive movements (bucking, interpreted as respiratory in origin). Chloroformed at 4.49. Autopsy showed recent hemorrhage overlying the cervical cord and over the vertex of the cerebral hemispheres. No trunk lesions found.

Guinea-pig No. 154 (sensitized). Given .75 cubic centimeter saline solution into same region as S_1. No symptoms.

Guinea-pig No. A (not sensitized). Given injection of .75 cubic centimeter horse serum near cervical cord as S_1. No symptoms.

The above experiment demonstrates the occurrence of irritative respiratory symptoms, with a slight admixture of both irritative and paretic non-respiratory symptoms on paraspinal injection of horse serum in the cervical region of sensitized guinea-pigs. This result may be contrasted with that in Experiment 2.

Experiment 2. Lumbosacral spinal cord. — Guinea-pig S_6 (sensitized by intraperitoneal injection of five cubic centimeters horse serum March 4, 1908), received at 3.15 May 2, 1908, .75 of a cubic centimeter of horse serum into the muscular tissue next the spine midway between tip of coccyx and the plane of iliac crests. One-half minute later respirations become markedly increased, subsiding shortly. At 3.35, crural paraparesis and simultaneous fore-paw biting movements. Chloroformed at 4.15. Autopsy negative, except for local muscular injury.

Guinea-pig No. 142 (sensitized Oct. 16, 1908, with 1/100 cubic centimeter horse serum subcutaneously) was anesthetized Jan. 5, 1909. Lumbar incision. At 11.30, three-quarters of an hour after recovery from anesthetic, received .3 cubic centimeter .9 NaCl near lumbar cord. (It may be noted in passing that in our experience complete ether anesthesia has no effect on the evolution of anaphylactic intoxication in sensitized guinea-pigs on the injection of horse serum into the brain. In this respect our findings agree with those of Rosenau and Anderson and disagree with the claims of Besredka. Animals on whom trephinings were performed under anesthesia for the purpose of subsequent localized injections into the nervous system were, however, allowed to recover fully before the serum injections were made.) No symptoms except disinclination to move when touched, a few shivering movements, and occasional whining. At 11.44, received 1+ cubic centimeter horse serum in the same region and at 11.46 coughed, showed respiratory distress, rolled about, twitched, showed brief clonic spasms of hind legs. Heart regular and strong. Respiratory distress increased, supplanted later by infrequent gasps. Death at 11.49, limbs flaccid, pupils dilated. Autopsy: pulmonary emphysema, a few small hemorrhages in lungs, no other gross lesions.

Experiment 2 exhibits two types of functional effect of paraneuraxial injections near the lower end of the spinal cord, in the first case very few respiratory symptoms and the simultaneous occurrence of paretic (lumbar) and irritative (brachial) symptoms, and in the second case a severe respiratory effect with simultaneous irritative (lumbar) phenomena. Incidentally, No. 142 shows the negative effect of salt solution injections in the same region.

In some instances a purely irritative effect was produced.

Experiment 3. Lumbosacral spinal cord. — Guinea-pig S_5 (March 4, 1908), sensitized by intraperitoneal injection March 4, 1908, received at 2.20 P.M. May 9, 1908, one cubic centimeter horse serum to left of coccyx. Immediate excitement, rearing (interpreted as respiratory), licking of old wounds on back (injuries received from guinea-pigs in cage). A little later flattened down on belly for a brief interval (only possibly paretic symptom noted). Quiet. At 2.30 began to wipe snout with paws, shook body violently many times as if to shake off wet; gnawed sides of basket. Complete recovery at 3 P.M.

Control. Normal Guinea-pig No. 153 given .75 of a cubic centimeter to left of coccyx. No symptoms.

In other instances an almost purely paretic effect was produced.

Experiment 4. Thoracic spinal cord. — Guinea-pig No. 119, sensitized Oct. 12, 1908, by subcutaneous injection of 1/100 cubic centimeter horse serum, was anesthetized at 3.40 Oct. 27, 1908. Median incision over thoracic spine. At 4.50, on recovery, received .25 cubic centimeter horse serum in region of thoracic cord. At 4.52, urination, progressive loss of power in hind legs. Crural paraplegia till 5.12, when improvement set in with biting movements. At 5.40, crural weakness. October 28, not abnormal. Received .25 cubic centimeter in motor cortex after trephining, but proved refractory.

It is obvious from the above four experiments that paraneuraxial injections at points adjacent to and remote from the respiratory central apparatus will produce a variety of symptoms. Respiratory symptoms are likely to occur after injection anywhere about the cord. Local (brachial or crural) symptoms correspond rather closely with the region of injection. It is not easy to predict whether the symptoms will be irritative, paretic, or mixed. The duration and course of these symptoms are also not yet predictable. We may compare these paraneuraxial injections with intravascular injections; although the surfaces bathed by the cerebrospinal fluid are far less extensive than the tissues reached by the blood, nevertheless there is considerable uncontrollable variation in the amount and rate of absorption both into and out of the fluid spaces surrounding the nervous system. Experiments to be detailed below show that post-orbital serum injections in sensitized guinea-pigs are more immediately and constantly symptom-producing and even fatal, for the reason that considerable serum is thrown directly into fluids in contact with the bulb.

Experiment 5. Post-orbital route. — Under this experiment we may adduce three guinea-pigs, Nos. 20, 21, 22, which were sensitized by subcutaneous injection of 1/100 cubic centimeter horse serum, Jan. 8, 1908, received 1/20 cubic centimeter horse serum by subconjunctival post-orbital injection Jan. 30, 1908, and died: No. 20 in convulsions in four minutes (hemorrhages of heart wall, lungs, liver), No. 21 in two minutes (minute hemorrhages of lungs, heart ?), No. 22 in four minutes (hemorrhages of lungs).

If death is delayed somewhat, emphysema of the lungs becomes prominent.

Experiment 6. Post-orbital route. — Guinea-pig No. 118, sensitized by subcutaneous injection of 1/100 cubic centimeter horse serum Oct. 12, 1908, received on Oct 27, 1908, at 4.22, about one cubic centimeter horse serum by post-orbital injection. Death in six minutes with marked emphysema.

Control animals in large numbers have been injected by this route by each of the writers for various purposes (experimental encephalitis, tests of anaphylactic and toxic substances), and no instance of sudden death has been recorded.

In cases where absorption is slower and but a small amount of horse serum is thrown directly into the fluid spaces at the base of the brain, a different set of symptoms will appear.

Experiment 7. Cerebral dura mater. — Sensitized Guinea-pig No. 57. Oct. 8, 1908, etherized, trephined in median line one centimeter anterior to occipital protuberance. While under ether, 4 gtt. diluted horse serum (horse serum two parts, 165 NaCl three parts) was applied to exposed dura mater. After ten minutes irregular generalized twitchings of clonic character, spasticity of extremities, with an approach to *flexibilitas cerea*. These symptoms lasted for twenty minutes. On emergence from anesthesia, restlessness, aimless movements, flaccidity except when grasped.

About two hours later, 5–6 gtt. horse serum (diluted as above) was injected in a backward direction into the brain, and death followed in nine minutes (hemorrhages in heart wall and (slight) lungs; stomach congested).

In other instances, respiratory effects may be produced by dural applications. In Experiment 8 both the respiratory and the non-respiratory nervous type of effect were secured by successive applications.

Experiment 8. Cerebral dura mater. — Sensitized Guinea-pig No. 29. Oct. 9, 1908, prepared and operated on like Guinea-pig No. 57 (v. Experiment 7). An hour after stopping anesthetic, a pledget of cotton soaked in horse serum was applied to dural surface. Respiratory symptoms in three minutes. Eight minutes later horse serum was directly applied to the dura, and in about three minutes mild non-respiratory nervous symptoms appeared which continued until the guinea-pig was chloroformed three hours later.

SUMMARY OF WORK ON PARANEURAXIAL INJECTIONS. — Injections of horse serum alongside the nervous system in sensitized guinea-pigs produce death probably in the same way as injections by way of the blood stream. From the rapidity of death by each method of injection (intravascular and paraneuraxial), it seems possible to conclude that the manner of access of the intoxicating substance to the respiratory centers is relatively unimportant.

The paraneuraxial route, like the intravascular, is a route by which more serum can gain rapid access to the respiratory centers than can happen by such routes as the subcutaneous or intramuscular. The intraperitoneal method of injection, also more severe in its effects than the subcutaneous method, undoubtedly permits rapid absorption of serum by way of the lymph apparatus in the diaphragmatic serosa and elsewhere.

But the intoxication following anaphylaxis is more than a respiratory intoxication, and the paraneuraxial route of injection brings out a multiplicity of irritative and paretic non-respiratory phenomena.

The irritative phenomena may be placed in two groups. The first group includes symptoms which can hardly be regarded as spontaneous in origin, such as clonic spasms of limbs, sudden and continual nipping of fore-paws, sudden and continued snout-wiping. Another group of more doubtful character attains considerable importance when associated with the former and when closely related in point of time with a toxic injection. Here may be placed certain muscular twitchings, *flexibilitas cerea*, sudden licking of healing wounds (induced hyperesthesia), generalized shaking of body ("as if to shake off wet," due to paresthesia?), sudden and persistent gnawing of sides of basket, restlessness, aimless rapid movements, heightened general excitability.

The paretic phenomena of non-respiratory origin include spastic crural paraplegia, flaccidity and paresis of limbs (flattening down of animal on belly). It is doubtful where to place sudden urination and dilatation of pupils.

The explanation of these effects of paraneuraxial injections is not as easy as first thought suggests. It is obvious that absorption of horse serum by various parts of the nervous system is responsible in some way for the several effects displayed. It is possible (though not probable) that absorption from the paraneuraxial fluids into the blood may be a necessary intermediary step in the production of some effects. It seems unlikely that enough horse serum can be absorbed from small vessels at the point of injection or in the field of operation to produce the rapid and violent effects following, *e.g.*, post-orbital injection. It seems wise, therefore, at least provisionally, to conclude that the paraneuraxial route of intoxication is separate from the vascular route.

There is, however, a possibility not yet considered which might alter our conception of the nature of these paraneuraxial intoxications. It is just possible, namely, that the peripheral nerve routes in their subdural courses should be the first to receive the toxic horse serum and should through one or more reflex arcs acting by familiar physiological means influence other centers, notably the respiratory center. Our paraneuraxial injections, consequently, served directly to bring up the problem of peripheral nerve intoxication.

The peripheral nerves, on almost any hypothesis and especially on the dualistic or anaphylactin hypothesis of Gay and Southard, must naturally share to a degree in the general sensitization, which is the result of the first injection of horse serum. We have undertaken to determine the degree of this hypothetical peripheral nerve sensitization. Incidentally, we have repeated the vagus nerve experiments of a former paper. The novel experiments were confined to the trigeminus, a nerve especially sensitive in the guinea-pig (compare the data of Brown-Séquard's Epilepsy), and the sciatic nerve, chosen as an easily accessible limb nerve. The negative results of trigeminus and sciatic experiments indicate that peripheral nerve (paraneural) absorption is of little or no importance in this connection. The paravagal injections have never yet yielded such fulminating results as paraneuraxial or intraneuraxial injections. Before considering the differences between the results of paraneuraxial and intraneuraxial toxic injections, we may give the details of our paraneural injections.

VAGUS EXPERIMENTS. — In the determination of the effects of horse serum on the peripheral nervous system the vagus nerve was first studied and the following seven observations adduce evidence to show that the toxic effect manifested is due to a local activity in already sensitized cells.

9. Guinea-pig No. 68. — Given .01 cubic centimeter horse serum

subcutaneously March 13. On April 8, left vagus isolated, a glass rod covered with cotton was put under the freed nerve and a pledget of cotton soaked in horse serum was applied to the vagus. There were immediate respiratory symptoms; subsequently, there were general irritative phenomena. Chloroformed. Autopsy showed marked emphysema of the lungs and one small hemorrhage in the fundus of the stomach.

10. Guinea-pig No. 75. — Given .01 cubic centimeter horse serum subcutaneously March 13. April 11, left vagus isolated and held over a piece of cork; .9 NaCl solution applied. No symptoms. After a short interval horse serum was applied directly to the nerve on a pledget of cotton. In one minute respirations were increased. Spasmodic contraction of the thorax. After one and a half minutes horse serum pledget removed. Animal complained continuously. On the floor continued to twitch for almost a half an hour. Chloroformed. At autopsy no lesions observed.

11. Guinea-pig No. 89. — Normal animal. April 11, left vagus isolated over a piece ofcork and touched with a pledget of cotton soaked in horse serum. No symptoms.

12. Guinea-pig No. 107. — Given .01 cubic centimeter horse serum subcutaneously Aug. 25, 1908. On October 20, left vagus isolated; .9 per cent NaCl solution applied to the nerve. No symptoms. After an interval of a few minutes horse serum applied to the nerve by means of a cotton pledget. Slight increase in frequency of respirations and later clonic twitching of both fore-legs which lasted for only a short time.

13. Guinea-pig No. 134. — Given .01 cubic centimeter horse serum subcutaneously Oct. 16, 1908. Nov. 4, 1908, left vagus exposed; .9 NaCl soaked in cotton applied to the vagus and allowed to remain for five minutes. Animal much the same as before; .9 NaCl now removed and horse serum applied. Animal restless, respiration rapid. (It was impossible owing to the animal's restlessness to determine exactly the increase in rate of respiration).

14. Guinea-pig No. 131. — Given .01 cubic centimeter horse serum subcutaneously Oct. 16, 1908. Jan. 4, 1909, left vagus exposed. Horse serum soaked in cotton applied. After three minutes there was an increase in irregularity of respiratory rhythm and the rate of respiration increased from fifty per minute before horse serum was applied to seventy-two per minute within seven minutes after the application of horse serum.

15. Guinea-pig No. 136. — Given .01 cubic centimeter horse serum subcutaneously Oct. 16, 1908. Jan. 4, 1909, vagus exposed; .9 NaCl on cotton applied to the vagus. Animal showed some struggling and twitching of the body, which continued after the saline was removed. Respiration during period when .9 NaCl was resting on the vagus were sixty per minute. After one and a half minutes saline removed and horse serum at once applied on cotton. Animal restless, struggling and whining as before, but respirations are now seventy per minute and show definitely more irregularity in rhythm.

From these experiments it may be concluded that horse serum stimulates the isolated vagus in a sensitized guinea-pig; the action manifests itself in a functional disturbance shown not only by an increase in the respiratory rate but also by a marked irregularity in its rhythm. The disturbance in the rate can be readily determined and is not seen in animals when normal salt solution (.9) is applied in sensitized animals, nor is it in evidence when horse serum is applied to the vagus of normal guinea-pigs. That there is under any circumstance a definite increase in respiratory rate in animals after operation is to be expected, but this can readily be differentiated from the symptom of respiratory irritation here seen, if the horse serum be not applied to the vagus until the animal has become quiet. The respiratory rate should be taken more than once and by more than one observer, as was done in these experiments.

The autopsy findings in these animals in the vagus experiments showed very marked emphysema. In no instance did the procedure cause the death of the animal, and it seems improbable that stimulation of the respiratory center through peripheral irritation of the vagus is sufficient to produce a fatal result.

TRIGEMINUS EXPERIMENTS (Experiments 16 and 17):

16. Guinea-pig No. 104. — Given .01 cubic centimeter horse serum subcutaneously Aug. 25, 1908. Oct. 16, 1908, given .5 cubic centimeter of .6 saline into subcutaneous tissue of upper jaw in similar region to that in animal No. 103. No marked symptoms. Animal restless and nervous.

17. Guinea-pig No. 103. — Given .01 cubic centimeter horse serum subcutaneously Aug. 25, 1908. Oct. 16, 1908, given .5 cubic centimeter horse serum subcutaneously into left upper jaw. Animal restless. No special symptoms.

SCIATIC NERVE EXPERIMENTS (Experiments 18 and 19):

18. Guinea-pig No. 128. — Given .01 cubic centimeter horse serum subcutaneously Oct. 16, 1908. Nov. 2, 1908, anesthetized; left sciatic nerve exposed. Ether stopped at 3.22 P.M. At 4.03 P.M., when animal had quite recovered from anesthetic, cotton soaked in horse serum was applied to exposed sciatic. No special symptoms. Animal whining and restless.

19. Guinea-pig No. 127. — Given .01 cubic centimeter horse serum subcutaneously Oct. 12, 1908. Nov. 2, 1908, anesthetized; left sciatic nerve exposed. Ether stopped at 3.10 P.M. At 4.10 P.M., when animal had thoroughly recovered from the effects of the anesthetic, cotton soaked in .9 NaCl was applied to sciatic. No symptoms other than those noted in case of animal No. 128.

INTRANEURAXIAL INJECTIONS. — Our endeavor to learn the nature of the differences in effect between intravascular injections and injections permitting dilution of the toxic horse serum in the cerebrospinal fluid (paraneuraxial injections) led to the consideration whether or not the toxicity of these paraneuraxial injections could depend upon absorption of horse serum by the nerves, suspended for a part of their course in the cerebrospinal fluid. Preliminary experiments (detailed in the previous section) by the paraneural route indicate that the direct absorption of horse serum by the nerves can be safely neglected as a factor in the fulminating symptoms which we can produce by injections directly into the fluids bathing the nervous system. Even soaking the vagus of a sensitized animal in horse serum fails to produce death or even the violent symptoms which characterize animals injected paraneuraxially.

In our search for an adequate conception of these paraneuraxial injections, we are therefore naturally led to direct injections into nerve tissues (intraneuraxial injections). Of course we are here confronted by the complicating features of coarse local injury, inevitable in the introduction of syringes and sometimes hard to avoid in trephining operations But these complicating features are absolutely prejudicial to the experiments only in the instance of intrabulbar injection, though they must be seriously considered in intracerebellar work.

We were able to establish by a very few experiments that the different anatomical divisions of the nervous system yielded quite disparate results upon injection.

Even in experiments fatal to the animals in the critical phase, both the respiratory and non-respiratory phenomena can readily be distinguished.

Experiment 20. Intraneuraxial, cervical spinal cord. — Guinea-pig No. 116 sensitized subcutaneously with 1/100 cubic centimeter horse serum Oct. 12, 1908. Oct. 27, 1908, etherized. Median dorsal incision. Ether removed 11.45. Good recovery. 12.20, received .25 cubic centimeter horse serum mixture (equal to 1/20 cubic centimeter pure horse serum) in cervical cord. Pronounced respiratory symptoms at once, with gaping movements. Twitching of all extremities, followed rapidly by brachial paraplegia (reflexes preserved) and later by flaccidity of all extremities. More marked respiratory symptoms. Death in six minutes.

In the case of the cerebellum, it is necessary to distinguish between the effects of direct mechanical interference (by destruction of tissue or pressure by clot) and the genuine effects of the horse serum.

The local effect of saline injections is shown in the following example:

Experiment 21. Intraneuraxial, cerebellum, control injection with saline solution. — Guinea-pig No. 73 sensitized subcutaneously with 1/100 cubic centimeter horse serum March 13, 1908. Oct. 14, 1908, etherized, cerebellum prepared for injection. Ether stopped 11 20 A.M. Received .5 cubic centimeter .6 per cent saline solution in left cerebellar hemisphere at 12.23 P.M. Animal fell on left side and turned about rapidly with head bent back and extremities at first moving clonically, later held tonically. When placed on back, tonic posture is supplanted in the hind legs by clonic movements. Later the tonic posture alternated with clonic movements (animal still lying on the side of injection). Recovery with ability to stand at 12.34. Disinclination to move. 12.45, some generalized tremors. Recovery, 2 P.M.

One hour later this guinea-pig was found sensitive and was killed in six minutes by injection of .5 cubic centimeter horse serum injected near bulbar respiratory center.

So far as the cerebellar symptoms (contractions of head and limbs) of Experiment 21, are concerned, it is equally possible to produce them by injections of either saline solution or horse serum into either non-sensitized animals or sensitized animals, as we have demonstrated by control tests not necessary to specify.

Two phenomena of neurological interest we have so far found only in sensitized guinea-pigs on intracerebellar injections with horse serum — opisthotonus and nystagmus. The following experiment illustrates these signs:

Experiment 22. Intraneuraxial, cerebellum. — Guinea-pig No. 91 sensitized intraperitoneally with seven cubic centimeters horse serum, July 23, 1908. Oct. 13, 1908, etherized. Ether removed 11.13 A.M., trephined over cerebellum in mid-line. 11.45, reeling and whirling movements upon injection of .5 cubic centimeter of .6 per cent saline solution. Cerebellar symptoms wholly ceased by 12.15 P.M. Injection of .5 cubic centimeter horse serum in same region produced pronounced cerebellar symptoms, but also nystagmus, twitches and jerkings of forelegs, dyspnea, and a phenomenon regarded as opisthotonus. The dyspnea seemed about to prove fatal. The eyes were kept turned upward. The conjunctival reflexes were never lost. Improvement in breathing, persistent dulness. Recurrence of whirling movements, animal lying on left side, with occasional quick violent clonic movements of fore limbs or of both fore and hind limbs. Later tonic spasms of all limbs except right fore limb, which showed irregular clonic twitchings. Death at 4.05, three hours and fifty minutes after injection of horse serum.

The protracted course of symptoms in the above experiment is another feature which we have several times noted following intracerebellar injections, but so far have been unable to prove that it is a special feature in the intoxication of sensitized animals.

The opisthotonus forms an important field of inquiry. It seems to be an irritative phenomenon, judging by its occurrence simultaneously with brachial twitchings and severe dyspnea. It is surprising that this symptom does not occur more often in guinea-pig diseases in general, since there is a pronounced, if not constant, tendency for the cervical region of the guinea-pig spine to bend with concavity upward when the spine is isolated from the trunk muscles at autopsy. However, it does not seem possible to consider this symptom purely a cerebellar symptom, especially as it is apt to occur when there is certain evidence of irritation of the cervical cord (dyspnea and brachial contractions).

Nystagmus is a symptom often shown in cerebellar disease in man (for example, in multiple sclerosis), although there appears to be doubt, in the interpretation of human data, whether the symptom is not rather to be attributed to lesion of the restiform body. Our experiments do not so far permit the solution of this problem.

The results of intracerebral injections of horse serum in sensitized guinea-pigs are striking. In 1908 we reported only paraneuraxial and not intraneuraxial injections. Meantime Besredka[20] had published work dealing with so-called intracerebral injections, proposing indeed to test the toxicity of diphtheria antitoxin by this method. But Besredka fails to note the place of injection in the brain, thus neglecting a crucial point in any determination of toxicity according to symptoms. It is certainly not a matter of indifference what part of the brain the syringe reaches, if we are to interpret results of injections by the ensuing respiratory or other muscular symptoms.

Very possibly many of the intoxications secured by Besredka are in reality paraneuraxial intoxications due to drenching of the respiratory center by serum spreading directly through the paracerebral fluids.

However this may be, our own more exact experimentation has shown not only that intracerebral injections have markedly different effects from those produced by intracerebellar or intrabulbar injections of horse serum in sensitized guinea-pigs, but also that a certain degree of functional differentiation can be proved to exist in the cerebral cortex of the guinea-pig, a functional differentiation in part quite comparable with that demonstrable by electrical stimulation. Furthermore, we have proved that intracerebral injections are decidedly less fatal to guinea-pigs than paraneuraxial injections (*e.g.*, by way of orbit).

Control tests show that injections of saline solution or of horse serum, or successive injections of both substances into the motor part of the non-sensitized guinea-pig cortex, even into the motor cortex as defined electrically (*e.g.*, by Ferrier in 1876[21]), fail to produce any form of symptoms.

Compare such negative results of control tests with the following:

Experiment 23. Intraneuraxial, cerebrum, motor cortex. — Guinea-pig No. 125. Sensitized subcutaneously with 1/100 cubic centimeter horse serum Oct. 12, 1908. Oct. 31, 1908, etherized and trephined over right motor cortex, 11.10 A.M. Ether removed 11.15. At 12.32 P.M. received 1/20 cubic centimeter horse serum directly below surface of motor cortex. Symptoms immediate: jerking of numerous trunk and limb muscles and irregular clonic spasms of muscles on both sides of body. The convulsions ceased and were replaced by extreme motor irritability. No respiratory symptoms subsequent to injection. At 12.50 P.M., weakness of left hind leg, persistent for two days, but on the second day (Nov. 2, 1908) much less marked.

With respect to the bilateral character of the muscular movements (except in the case of the paresis), we may suggest that the absence of the falx cerebri in the guinea-pig may readily permit absorption of materials by both cortical centers, and that in any case the two centers and their conducting paths are very close together.

Injections of 1/20 cubic centimeter horse serum by way of the orbit are in our experience certain to kill sensitized guinea-pigs. Injections of 1/20 cubic centimeter horse serum into the motor cortex consistently fail to kill sensitized guinea-pigs. We have seen one sensitized guinea-pig die after receiving about .3 cubic centimeter horse serum in the cortex, but injection of .5 cubic centimeter in another instance failed to kill. Injections of larger amounts are for mechanical and spatial reasons likely to permit drenching of paracerebral spaces with serum and consequent ready approach to the respiratory centers. In this way we should endeavor to explain Besredka's toxic intracerebral injections, and should recommend those working on his lines to employ the orbital method of injection.

On account of occasional uncontrollable leakage into the paracerebral spaces or even pricking the wall of the lateral ventricle by the syringe, the chance of direct drenching of the medulla is always to be considered in such experiments.

We have no tests at present to report bearing on the detailed mapping out of the guinea-pig cortex from the standpoint of anaphylactic intoxication. These details and their relation with the data of electrical stimulation (*e.g.*, of Ferrier) will require special precautions and extirpation experiments.

We are prepared, however, to demonstrate a differentiation of cortical reactions (viz., into purely motor and, very probably, sensori-motor reactions), which indicates the direction that such neurophysiological work must take. The variety of clinical symptoms, over and above the purely respiratory symptoms, which sensitized guinea-pigs show when intoxicated, is theoretically explainable upon these lines, that is, as due to the irritation of various properly prepared motor and sensori-motor centers, over and above the respiratory center.

To demonstrate this special sensitization of a non-motor portion of the guinea-pig cortex, we have carried out tests with the olfactory region, regarding as olfactory the lower anterior portions of the cerebral flank which come into relation with the olfactory tracts and which possess a histological differentiation similar to that of the smell area in man. We have injected several of the areas outlined by Ferrier. Control injections of saline solution in these areas occasionally produce nose-rubbing movements doubtless of mechanical origin (resembling various movements elicitable with electrical stimulation), so that the same caution has to be employed in this region as in intracerebellar work.

The following experiment illustrates this point, together with a negative control injection with saline solution:

Experiment 24. Intraneuraxial, cerebrum, olfactory region. — Guinea-pig No. 141. Sensitized subcutaneously with 1/100 cubic centimeter horse serum Oct. 16, 1908. Jan. 5, 1909, etherized and trephined over right olfactory cortex. Ether removed, 10.35 A.M. Received .25 cubic centimeter .9 saline solution in cortex, 11.35 A.M. No symptoms. Received about .25 cubic centimeter horse serum in same region, 12.10 P.M. Symptoms appeared suddenly in four minutes: bending downward of nose, pawing at nose and nose-rubbing movements with fore-paws, occasional head-shaking movements. These movements would cease sharply and then suddenly recur. During the quiet intervals, back was held arched and limbs were occasionally drawn together. There was an infrequent single twitch or shudder of the whole body. All symptoms disappeared within half an hour.

Such tests are naturally difficult of interpretation, in common with all similar supposedly sensori-motor tests, even such as are effected by electrical stimulation. The anaphylactic intoxication here exhibited resembles that in the cerebellum, in that it differs only quantitatively and in certain qualitative respects (such as onset and duration) from non-anaphylactic intoxication, such as may be brought about by mechanical means in non-sensitized animals.

We are disposed, however, despite difficulties of interpretation, to insist on the peculiar excitability of the motor and sensori-motor (olfactory) cortex in the sensitized guinea-pig when stimulated by local injections of horse serum.

The theoretical significance of varying the locus of the toxic injection is brought out sharply. Whereas death is practically constant and exceedingly rapid when the paraneuraxial spaces are drenched by orbital injections, death is infrequent when intraneuraxial injections are made in any non-respiratory part of the central nerve substance. Death occurred, for example, in only one in nine of motor cortex injections, and in a similar small percentage of olfactory injections. In these fatal instances, moreover, it is not easy to exclude the complicating accident of paraneuraxial drenching by leakage of serum.

SUMMARY AND REMARKS.

The work of Gay and Southard upon the localization of cell and tissue anaphylaxis (serum type) in the guinea-pig has been continued. The work of 1908 had brought out sharply the strict comparability of intravascular and orbital injections in their capacity to produce violent respiratory symptoms or death. As was then stated, " The occurrence and rapidity of death in the critical phase, as well as the severity of respiratory symptoms throughout the toxic phase, appear to vary with the nearness of the toxic injections to the respiratory central apparatus."

But evidence was further adduced to show that the sensitization of the respiratory centers was but relative and that those who claim that the toxic effects are due to a specifically respiratory toxin are inexact.

The theoretical significance of injections alongside the nervous system (paraneuraxial injections) was shown to consist in the capacity of such injections to spread directly through the cerebrospinal fluid to the respiratory centers.

Such direct paraneuraxial drenching of the sensitized nervous system was shown both theoretically and experimentally to be approximately equivalent to intoxication by the intravascular route.

The evidence from paraneuraxial injections has now been strengthened and so supported by evidence from several kinds of intraneuraxial injections as to warrant confirmation of our tentative statement of 1908 "that differential irritative and paralytic reactions can be secured by small localized injections of horse serum adjacent to various parts of the sensitized central nervous system."

The most lethal form of paraneuraxial injection is the orbital. The orbital method of injection is the method of election for determining toxicity, in Besredka's sense, since the complicating features of intravascular injection and of trephining are avoided. The orbital method permits immediate drenching of the bulb through the cerebrospinal fluid.

Many varieties of paraneuraxial injection have been practised. To secure non-respiratory phenomena and avoid lethal outcome, it is only necessary to inject the serum into the muscular and interstitial tissues outside the nervous system, thus permitting a slower absorption and a differentiation of results analogous to that secured by comparative intraperitoneal and subcutaneous injections.

Both irritative and paretic non-respiratory symptoms can be produced by paraneuraxial injections of various dosage appropriately localized.

It is not probable that these paraneuraxial injections act by intoxicating the nerves suspended in the cerebrospinal fluid; at any rate no comparable degree of intoxication has been secured by paraneural applications of serum outside the enclosing sheath of the central nervous system (trigeminus, sciatic nerve). Nor has death ever followed applications to the vagus in its extradural course despite the production of severe respiratory symptoms thereby.

Intraneuraxial injections (*e.g.*, intracerebellar, intramyelic, intracerebral) in sensitized animals effect a variety of symptoms, sometimes irritative, sometimes paretic. It is easy to distinguish respiratory and non-respiratory phenomena.

Intramyelic injections in the cervical region produce not merely the expected respiratory symptoms but also brachial paraplegia.

The effects of intracerebellar injections must be interpreted with caution, on account of symptoms producible by purely mechanical means. Opisthotonus and nystagmus appear to be characteristic of anaphylactic intoxication. But with respect to nystagmus, the proximity of the restiform body and of the corpora quadrigemina must be considered.

Intracerebral injections produce a variety of symptoms, such that the locus of injection becomes important to consider. We are able to distinguish a motor from a sensorimotor (olfactory) type of reaction. These observations open a field of considerable neurological interest, since heretofore electrical stimulation in normal animals has been the best means of attack on localizing problems. Obviously extirpation experiments before and after sensitization and subsequent anaphylactic intoxication will unearth many novel facts.

We are not disposed to emphasize unduly the dualistic or anaphylactin hypothesis of Gay and Southard as applied to the phenomena of anaphylaxis. We would only once more call to the attention of the supporters of the antibody hypothesis how much more difficult that hypothesis becomes in case the alleged antibodies are intracellular and lodge in varying degree in different loci of the nervous system as well as elsewhere in the body.

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Acute Encephalitis and Brain Abscess

XXI

by

E. E. Southard

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CHAPTER XV.

ACUTE ENCEPHALITIS AND BRAIN ABSCESS.

By E. E. SOUTHARD, M.D.

ENCEPHALITIS.

Synonyms.—Inflammation of the brain; acute red softening of brain; brain fever; cerebral fever; cerebritis; phrenitis; phrenesia; phrenetiasis; phrenicula; cerebral phlegmasia; *calenture; febbre perniciosa frenetica; suppuratio occulta cerebri.* The terms brain fever, cerebral fever, and the like frequently refer to meningitis. Conversely, discussions of meningitis frequently contain data concerning encephalitis. Papers on meningo-encephalitis, encephalomeningitis, poliencephalitis, leukencephalitis, encephalomyelitis, poliencephalomyelitis, mycosis of brain, as well as those on brain abscess, hyperæmia and congestion of the brain, pernicious malaria, central neuritis, softening of the brain, and encephalomalacia contain pertinent material.

Definition.—Encephalitis means inflammation of the encephalon or brain. The best usage includes under the term encephalitis exudative inflammations of the brain. This usage has been adopted in the present description, which consequently excludes all those instances of so-called encephalitis in which degeneration, atrophy, and other non-exudative processes are paramount. Many processes described in the literature as encephalitic would be more accurately described under the generic term *encephalopathy.* Accepting this nomenclature, we should regard *encephalitis* (due, for example, to the toxins of the *Staphylococcus pyogenes aureus*) as a subordinate class under encephalopathy, coördinate with, although distinct from, such other subordinate classes of brain disease as *encephalic trauma* (*e. g.*, laceration of brain), *encephalomalacia* (focal type due to vascular plugging), and *encephalic degenerations* (*e. g.*, *encephalopathia saturnina*). The literature contains many references to the above-mentioned subordinate classes under the name encephalitis. Discussions of traumatic encephalitis, of lead and arsenical encephalitis, and (in the older writers) of encephalitis with cyst formation of vascular origin are not uncommon.

History.—Phrenitis is the term used by Galen for encephalitis. He calls phrenitis *delirium magnum et continuum cum febre acuta.* In fact, phrenitis appears to have been for Galen a delirium accompanied by continuous fever, whereas mania was a form of non-febrile delirium. *Phrenitis est inflammatio cerebri et meningum ejus, ob ebullitionem calidorum humorum, delirium magnum et continuum cum febre acuta inducens.* Paracelsus appears to have related both phrenitis and mania to the sublimation of mercury due to internal or external heat.

The title *De Encephalitide*[1] appears in medical literature at least as early as 1798 (T. N. Beels), and the title *De Phrenitide*[2] as early as 1615 (H. Petraeus), and these indicate the familiarity of the terms at that time. *Pseudophrenitis* and *paraphrosyne* were used in Petraeus for conditions in which the delirium is not continuous. In the seventeenth century no less than ten monographs appeared on phrenitis and allied topics, and no less than thirty-four in the eighteenth century. Monograph publication on these lines was especially frequent in the first two decades of the nineteenth century. The first systematic treatment of the subject in the modern sense was that of Hasse,[3] in 1855. But this suffers from the confusion, then prevalent, between the effects of vascular plugging and those of true inflammatory exudation.

Most of the work on encephalitis preceding the era of Virchow's work on thrombosis and embolism (1846) can be neglected for modern purposes. Virchow's work began to have wide currency in 1856, but, although it cleared the way for a definition of focal softenings (focal encephalomalacia), the status of encephalitis was no better than before. Nor can it be said that Virchow's contribution of *encephalitis neonatorum* (1867)[4] aided systematic work, since it was at once opposed by Hayem[5] (1868) and Jastrowitz (1870), and cannot yet be said to be a solved problem. Hayem (1868) developed the idea of non-suppurative or hyperplastic encephalitis. Various contributions followed in which the infectious character of encephalitis became probable. Huguenin (1876) contributed a faithful and acute discussion of encephalitis to von Ziemssen's *System*,[6] in which he was able to point out wholly characteristic differences between encephalitis and encephalomalacia, but in which he was far less successful in distinguishing between non-purulent and purulent encephalitis.

Wernicke,[7] in 1881, described the disease (*poliencephalitis acuta hemorrhagica superior*), which bears his name, as an acute inflammatory process about the Sylvian aqueduct region, and compared the process with acute anterior poliomyelitis. With the interest in infectious processes in the early eighties, Strümpell[8] (1884) was able to construct a very productive hypothesis—that many cases of cerebral palsy in children are due to encephalitis of the motor areas. In 1890 Strümpell was able to describe two cases of acute primary encephalitis in adults (autopsies by Zenker).[9]

In 1893 Macewen's work on *Pyogenic Infective Diseases of the Brain and Spinal Cord* appeared, in which the surgical importance of brain abscess and inflammation of otitic origin was developed. In 1895 Nauwerck[10] found an organism of the influenza group in encephalitis. In 1898 Councilman, Mallory, and Wright were able to describe and figure encephalitic lesions which were undeniably due to Weichselbaum's meningococcus, and were in all cases co-existent with frank meningitis.

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[1] T. N. Beels, *De Encephalitide*, Lugd. Bat., 1798.

[2] H. Petraeus, *De Phrenitide*, Marpurgi, 1615.

[3] *Handbuch der speziellen Pathologie und Therapie*, Erlangen, 1855, Band iv.

[4] *Arch. f. path. anat., etc.*, Berlin, 1867, xxxviii.

[5] *Etudes sur les diverses formes d'encéphalite*, Paris, 1868.

[6] Hirnentzündung. *Handbuch d. spec. Path.* (Ziemssen), Leipzig. 1876, Band xi.

[7] *Lehrbuch der Gehirnkrankheiten*, Kassel, 1881, Band ii, Th. 3, S. 229 to 242.

[8] *Jahrb. f. Kinderh.*, Leipzig, 1884, vol. xxii.

[9] *Deut. Archiv f. klin. Med.*, Leipzig, 1890, xlvii, 53 to 74.

[10] *Deut. med. Woch.*, Berlin, 1895, No. 25, p. 393 to 397.

The infectious character of several types of exudative inflammation of the brain is well established. But the complete natural history of encephalitis does not yet exist. Ten years after Huguenin's elaborate discussion, Bernhardt, in *Eulenburg's Real-Encyclopädie* (1886), was still able to say that no unitary picture could be presented, even of that kind of brain softening due to vascular occlusion. In 1904 Friedmann stated that recent distinctions of encephalitis into various forms are erroneous, and that all the phenomena of encephalitis can be produced by a great variety of agents, among which are the meningococcus, the influenza bacillus, embolism, aseptic trauma, corrosive substances, and heat.

The interest of the present day is in the bacteriology (parasitology?) of these processes and in the possibility of differentiating cases into groups according to their infectious origins. Clinically, we are as yet unable to define groups with precision according to the different known infective agents. For some years, in Boston, an effort has been made to correlate these points of view. This work started out from the report of Councilman, Mallory, and Wright on "Cerebrospinal Meningitis," and has taken the shape of several studies dealing with the histopathological and clinical effects upon the brain of the Micrococcus aureus (Southard and Sims,[1] Southard and Keene[2]), pneumococcus (Bullard and Sims,[3] Southard and Keene[4]), streptococcus (Southard and Stratton[5]), and *Bacillus typhosus* (Southard and Richards[6]). This work has shown the association of *Staphylococcus pyogenes aureus* and of the pneumococcus with acute hemorrhagic encephalitis, uncomplicated by meningitis.

Classification.—We distinguish the acute from the subacute and chronic forms of encephalitis. In the acute form we find characteristically the cardinal signs of inflammation. Of these signs, redness and swelling are prominent postmortem features of acutely inflamed brain tissue. The pain which sometimes accompanies encephalitis is due not to compression of the cerebral tissue itself, but to the pressure incidentally exerted upon the trigeminal endings by the swelling of the brain. Alterations of temperature can be demonstrated under surgical or experimental conditions only. More prominent and important than these signs is the so-called fifth sign of inflammation, or *functio læsa*, which may so affect consciousness at some stages as to remove the feature, pain, which is striking in inflammation elsewhere.

In the *subacute* and *chronic* forms we meet a variety of reactions which have, until recent years, been little understood. Both the histological findings and the clinical pictures in these latter forms have much in common with the degenerative class of encephalic disease. The terminal effect of repair in several classes of encephalic disease (inflammatory, traumatic, degenerative) is atrophy or induration (sclerosis, gliosis), or even porencephaly, which may offer few or no features to determine the nature of the original disease. These points partly explain why there has been so much confusion as to what the term encephalitis precisely denotes.

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[1] *Jour. Amer. Med. Assoc.*, 1904, xliii, 789.
[2] *Amer. Jour. Med. Sci.*, 1905, cxxix, 474.
[3] *Boston Med. and Surg. Jour.*, 1904, cli, 647.
[4] *Jour. Amer. Med. Assoc.*, 1906, xlvi, 13.
[5] *Ibid.*, 1906, xlvii, 1271.
[6] *Jour. of Med. Research*, 1908, vol. xix.

Topographically, we distinguish *encephalitis* from *neuritis* (inflammation of nerves) and *myelitis* (inflammation of spinal cord or medulla spinalis). Within the skull, we distinguish encephalitis from (*lepto*)*meningitis* (inflammation of the pia mater) and *ependymitis* (inflammation of the ventricular linings). Encephalitis means, then, strictly speaking, an inflammation of brain substance; but we habitually include also inflamed brain tissue in which there is little or no sign of parenchymal change and the chief sign of injury is perivascular infiltration. Within the brain substance, we might well distinguish between (and do so denominate certain diseases) *poli*(*o*)-*encephalitis* (inflammation of gray matter) and *leuk*(*o*)-*encephalitis* (inflammation of white matter).

Chronologically, we distinguish *acute encephalitis* (of which the types produced by staphylococci, streptococci, and pneumococci have been most studied), *subacute encephalitis* (of which the best examples are seen in syphilis and in tuberculous meningitis), *chronic encephalitis* (*e. g.*, healed cases of epidemic meningitis), and *progressive encephalitis* (perhaps of toxic character, as in dementia paralytica so often following syphilis). These latter forms are not considered in this article.

Since the differentiation of thrombotic from inflammatory softenings, the development of entities in encephalitis has been as follows:

Encephalitis congenita, Virchow, 1867.

Spontaneous hyperplastic encephalitis, Hayem, 1868.

Poliencephalitis acuta hemorrhagica superior, Wernicke, 1881.

Acute infantile poliencephalitis (infantile cerebral palsy), Strümpell, 1884.

Acute primary encephalitis (adults), Strümpell, 1890.

Pyogenic infective disease of the brain, Macewen, 1893.

Encephalitis (*Bacillus influenza*), Nauwerck, 1895.

Acute hemorrhagic encephalitis (*Staphylococcus pyogenes aureus*, pneumococcus), Southard and Keene, 1905 and 1906.

The most extensive experimental work on the pathogenesis has been by Friedmann. The most influential systematic treatise since Huguenin, 1876, has been Oppenheim's chapter in *Nothnagel's Handbuch*, 1897, now in its second edition (Oppenheim and Cassirer, 1907).

The etiological basis has, so far as possible, been adopted in the classification which follows:

Etiologically Well Characterized.—*Influenzal Encephalitis. Pyogenic Encephalitis.* (*Hemorrhagic Superior Poliencephalitis, alcoholic form.*)

Etiologically Doubtful, Clinically Definite.—*Acute Hemorrhagic Encephalitis, Strümpell type*, often pyogenic (?), sometimes influenzal (?), or unknown in origin. *Acute Bulbar Myelitis. Acute Encephalomyelitis. Rabic Encephalitis* (not considered in this article).

Etiologically and Clinically Obscure.—*Acute Non-suppurative Encephalitis, Hayem type. Encephalitis in the Newborn.*

To these must be added other forms of such rare occurrence as to forbid systematization. Thus, *Bacillus typhosus* (as well as other typhaceæ), *Bacillus anthracis*, and *Trichinella spiralis* have been found in encephalitis. The encephalitis following scarlet fever, measles, and other exanthems is probably of pyogenic origin. The relation of encephalitis to gonorrhœa, mumps, and whooping-cough is still doubtful etiologically. The encephalitis of tuberculous meningitis, of syphilitic meningitis, of sleeping sickness, and of paralytic dementia is of importance, but is not considered here.

Influenzal Encephalitis.—The great pandemic of influenza in 1889 to 1890 led a few writers (Leichtenstern, 1890, 1892; Fürbringer, 1892; Putnam, 1892)[1] to suspect the influenzal origin of encephalitis. Kraepelin contributed a paper on psychoses following influenza in 1890.[2] The influenza bacillus was cultivated by Nauwerck from a case of encephalitis in 1893–94. He found the bacilli in sections from a soft hemorrhagic spot in the cerebellum and in the sediment of the ventricular fluid. The organisms were cultivated from the ventricular fluid. Trouillet and Esprit[3] published in the same year a report of pure cultures from the ventricular fluid in a disease which they term *Meningo-encéphalopathie grippale.* It was suggested that influenza toxins might prepare the tissues for the invasion of other organisms, notably for the pneumococcus, which might be recovered in pure culture from the meninges or brain substance.

The atrium of infection in brain influenza may be: (1) The blood (formerly considered extremely rare); (2) the nasal mucosa and the cribriform plate; and (3) the lymphatics of the middle ear. The nasal mucosa is now considered to be the most frequent route of infection, but it is probable that influenza is frequently a blood infection. Pfuhl found three cases of influenzal encephalitis in an epidemic of 93 cases of influenza in the barracks at Hanover in 1895–96.[4]

Encephalitis is not, as a rule, part and parcel of an attack of typical influenza, but follows recovery or partial recovery from such an attack. Sometimes there is an interval of several weeks before cerebral symptoms set in. In fact, the previous attack of influenza may be quite forgotten or considered as a cold in the head. Oppenheim remarks that the premonitory symptoms of influenzal encephalitis may be hard to interpret, since the headache, vertigo, nausea or vomiting, apathy, drowsiness, and general weakness may be regarded as merely incidents in convalescence from ordinary influenza. In other instances the onset may be acute.

If there is anything which distinguishes this form of encephalitis, it is a gradually increasing loss of consciousness, taking several hours or a day for its completion. The patient can, as a rule, be roused by sharp stimuli, and the pupillary reflexes are normal. The projection system is not characteristically involved at the onset. Meningitic symptoms, such as stiffness of neck and opisthotonos, are exceptional. There is irregularity in the temperature, which is rarely high until the cerebral symptoms are well under way. Some of the febrile temperatures are perhaps due to intercurrent infections (Oppenheim). But these statements were made before the question of influenzal septicæmia had engaged attention. The pulse is likely to be slow at first, but before death quicker, small, and irregular.

The focal symptoms develop, as a rule, after coma has set in, not apoplectically, but one by one (Stadelmann's case with onset suggesting cerebral hemorrhage is a rare exception). Moreover, in a limb about to become paralyzed there are often premonitory symptoms, such as weakness, numbness, or convulsions. Sometimes the convulsions involve the whole side of the body, when the eventual loss of power is to be a monoplegia. The paralyses may be quite masked by coma, or a difference in the two sides may be detected by the occurrence of choreiform movements on one side only. The variety of onset and course in these cases is so great that Leichtenstern feels that there are limiting cases in which a hemiplegia may develop without coma on a truly influenzal basis. Almost every possible focal symptom has been described in cases of encephalitis developing *after* influenza; but motor symptoms far outnumber sensory ones.

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[1] On Multiple Neuritis, Encephalitis, and Meningitis after Influenza, *Boston Med. and Surg. Jour.*, 1892, vol. cxxvii.

[2] *Deut. med. Woch.*, 1890, xi.

[3] *Sem. Méd.*, 1895, No. 21.

[4] *Zeit. f. Hyg. u. Inf.*, 1897, Band xxvi.

It was formerly thought that the prognosis was grave, but Oppenheim is inclined to agree with Leichtenstern and Fürbringer that many patients recover. The relation of influenzal encephalitis to spastic infantile hemiplegia cannot yet be stated; probably many of these cases are the relics of early coccal infections following exanthems.

Pyogenic Encephalitis.—Macewen states that pyæmic abscess of the brain may arise from infective embolism originating from pneumonic areas, fetid bronchitis and empyema, fetid pericarditis, infective compound fractures, rarely acute infective periostitis, and occasionally infective ulcers of the intestines and abdominal cavity. In his experience abscesses were rarely multiple except when originating in pyæmia. Macewen makes mention of purulent encephalitis, red softening, and white softening. He describes purulent encephalitis as consisting of a swelling of the cerebral substance with extensive serous and leukocytal exudation and extravasation of red blood corpuscles, which he recognizes to be of very frequent occurrence in acute inflammations of the brain. The coalescence of minute hemorrhages gave rise to red softening according to Macewen. He made the observation that the pressure occasioned by the œdema and swelling of the brain "may *aid* in producing the pain experienced by the patient at the very outset of the encephalitis, especially when the ganglia of the fifth and its recurrent meningeal branches are included in the area of pressure."

White softening is described by Macewen as due to infective embolism. He regarded microörganisms as the chief cause of intracranial pyogenic processes, and emphasizes the middle ear as an atrium of infection. He found the Streptococcus pyogenes and the Staphylococcus aureus most frequently in brain abscesses and in suppurative leptomeningitis. Macewen does not, however, appear to have taken up non-surgical conditions systematically.

In pyogenic encephalitis there is an invasion (whether primary or secondary) of pyogenic bacteria. Although the pyogens in the broad sense include numerous bacterial species, in the writer's experience only the *Staphylococcus pyogenes aureus* and (in a few instances) the pneumococcus have produced pure examples of hemorrhagic encephalitis. Encephalitis complicated by meningitis or meningitis complicated by encephalitis (conditions usually united under the term meningo-encephalitis) are produced by the pneumococcus and streptococcus. In the writer's eight cases of pyogenic encephalitis the encephalitis was produced in six instances by *Staphylococcus pyogenes aureus* and in two instances by the pneumococcus. A novel and interesting possibility in the pathogenesis is an acute inflammatory lesion of the arachnoid villi of the longitudinal sinus.[1] If this could be shown to be the rule, one reason could be assigned for the frequent affection of the central gyri in this disease.

All the writer's cases of *Staphylococcus pyogenes aureus* brain infections have shown multiple hemorrhages in the brain. In two instances a condition which might be termed bacterial apoplexy has been produced in which rupture of a vessel and solution of surrounding brain tissue has been attended with intraventricular blood. Such a case occurred in a girl, aged twelve years, who had just recovered from diphtheria.

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[1] Southard and Sims, *Jour. Amer. Med. Assoc.*, 1904, xliii, 789.

The pneumococcus, although cultivated somewhat more frequently from the brain and meninges than the staphylococcus, is less likely to produce hemorrhagic encephalitis.

In general, it may be stated that this disease occurs at all ages. Cases ranging from five to fifty years occur in the writer's series of pure hemorrhagic encephalitis; cases of meningo-encephalitis range from four months to ninety years of age. Alcohol is an occasional antecedent factor. In children the exanthems frequently precede encephalitis, but encephalitis may appear to be a late complication of an exanthem. Arterial disease appears to have little or no relation to pyogenic encephalitis. The *onset* is more apt to be acute than gradual. The cases of gradual origin in the writer's series were more apt to be in older patients. The course is short, although variable, ranging from twenty-eight hours in a fulminant pneumococcus case to two weeks. The diagnosis of hemorrhagic encephalitis was not made in the writer's cases. The symptoms pointed to lesions of the brain in all cases except two, in which diagnoses of septicæmia and of acute disease of unknown origin were made. Meningitis was considered in two of the Staphylococcus pyogenes cases, and in one of these suspicion of poisoning was raised. In the cases of meningo-encephalitis the diagnosis of meningitis was frequent, and in 1 case a definite diagnosis of meningococcus meningitis was made. In 3 cases of meningo-encephalitis no other diagnosis than that of severe pneumonia was made. In the cases due to *Staphylococcus pyogenes aureus* the onset was sudden in 3 cases (hemiparesis and unilateral convulsions in 1; chilly feelings and frontal headache followed by ecchymoses in 1; malaise, manifold pains, ecchymoses, and cerebral symptoms in 1). In 1 case the symptoms gradually supervened upon a pleurisy and orbital suppuration. One case showed a gradual onset.

The syndromes, as a whole, were of pronouncedly cerebral type in 2 cases, of meningitic trend in 2 cases, of septicæmic character in 1 case. Septicæmia could be suspected in 3 cases in which superficial ecchymoses or suppuration became prominent. The temperature varied for the various cases; at times 103° and 104° for 2 cases; the temperature in 3 cases was never high and frequently subnormal. The pulse was in no case subnormal, and, as a rule, ranged from above 100. The respirations were, as a rule, increased.

The duration of the encephalitic symptoms cannot, in all cases, be closely reckoned; in 1 case three days; 1 case one week (after development of erysipelatoid condition) or three weeks (after injury to eye); 1 case, eight days; 1 case two weeks; 1 case fifteen days; 1 case unknown. Thus, those cases were of longer duration in which the cerebral syndromes were most clearly marked.

The distribution of the brain lesions was as follows: Four cases showed areas of frank and somewhat voluminous hemorrhage, as a rule involving primarily the subcortical region (the vertex in 1, the occipital lobes in 2, and in 1 the pons). Three cases showed multiple ecchymoses and small abscesses of the cortex or subcortical region, with or without gross evidence of surrounding œdema. In 3 cases œdema of the pia mater was noted. In 2 cases an effusion of blood into the lateral ventricles was noted; in these cases the convolutions were flattened.

In 2 cases, in which the temporal lobe was involved, the middle ears showed no lesion. The mucosæ of the head play no such role in this kind of encephalitis as in the massive brain abscesses made familiar by Macewen.

A remarkable association of encephalitis with focal pulmonary lesions was made out in this series. Pulmonary lesions were either grossly prominent or made microscopically in all six cases. It is possible that this association is a mere matter of coincidence.

Hemorrhagic Superior Poliencephalitis (Wernicke's Disease; Total Ophthalmoplegia; Nuclear Ocular Palsy; Alcoholic Ophthalmoplegia).—First described by Gayet, 1875,[1] as *affection encéphalique* (*encéphalite diffuse probable*), localized in the upper parts of the cerebral peduncles and in the optic thalami, as well as in the floor of the fourth ventricle and in the lateral walls of the third ventricle, the disease owes its name to Wernicke, whose cases were published in his *Lehrbuch* in 1881. The entity was further strengthened by Boedeker, who in 1892 summed up the findings in 11 cases (3 apparently non-alcoholic, and 8 alcoholic). The resemblance of the disease to Korsakoff's polyneuritic psychosis has been brought out by Bonhoeffer (1901).[2] Schröder has recently shown that the disease, although a definite entity, is actually not a true encephalitis in the exudative sense of the term.

Wernicke defined the disease as an acute inflammatory disease of the nuclei of the eye muscle nerves, leading to death in from ten to fourteen days. The disease was characterized by palsy of eye muscles of rapid onset, quickly progressing to almost complete ophthalmoplegia (sphincter iridis and levator palpebrarum excepted). The patient's gait recalled that of alcoholism, showing a combination of stiffness and ataxia. Somnolence was a striking feature, either at onset or toward the close. Where somnolence set in late, the disease at first recalled delirium tremens. Optic neuritis occurred in all Wernicke's cases. The course is not always so acute, for Gayet's case lasted five months, and other writers[3] described cases with recovery. The non-alcoholic and the alcoholic forms of Wernicke's disease are considered separately.

(*a*) *Hemorrhagic Superior Poliencephalitis, Non-alcoholic.*—These cases are very few. In Gayet's case the symptoms followed three days after a boiler explosion, in which, however, the patient, a man, aged twenty-eight years, sustained no bodily injury. Paraphasia and paragraphia were the first symptoms. General weakness, apathy, and marked *drowsiness* followed. The face became mask-like, and there was double ptosis with a general atony of the facial musculature, so that in speech there were no expressive facial movements. General weakness was such that the patient could scarcely stand or grasp objects. Pupils, vision, and all kinds of sensation were quite normal. There was almost complete *paralysis* of both *oculomotor nerves*. There was later transitory hemiplegia, which disappeared, leaving the patient in a state of excitement, with more facial expression and pain in the right leg. Conditions varied thereafter. Intelligence was maintained, and there were never any considerable changes in the eye grounds. Emaciation followed with incontinence and decubitus; death occurred five months after the accident.

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[1] *Archives de Physiologie*, 1875, vol. vii.

[2] *Monatsschr. f. Psych. u. Neur.*, 1899, v, 265.

[3] Wolfe, *Jour. of Nerv. and Ment. Dis.*, 1894; Wiener, *Brain*, 1897, xx, 458.

Morbid sleepiness also characterized Wernicke's first case, a young girl, who had attempted suicide with sulphuric acid. The sleepiness, ataxia, optic disturbances, and vertigo came on two months after the suicidal attempt. Oculomotor palsy, disorientation, and hebetude were the main features of the attack, which led to death twelve days after the onset. Salomonsohn's case showed loss of knee-jerks and slowing of the pulse, in addition to other characteristic symptoms. Luce's case was incidental in miliary tuberculosis. Murawieff's case followed three months after influenza, and showed also sarcoma of one precentral gyrus. Zingerle's case had chronic digestive disturbances and an abdominal tumor of long standing.

(*b*) *Hemorrhagic, Superior Poliencephalitis, Alcoholic.*—Alcoholic ophthalmoplegia is a disease closely allied in symptomatology with Korsakoff's disease and with alcoholic polyneuritis. Some writers believe that the symptoms in these three conditions scarcely represent entities, but are all incidents in chronic alcoholism. If this be true, it is doubtful whether Wernicke's disease is truly encephalitis in the exudative sense, and, in fact, Schröder was able to find in a typical case, merely, (*a*) destructive lesions due to minute hemorrhages, and (*b*) reparative changes (phagocytic cells, vascular and neuroglial changes) like those following any non-inflammatory injury. Schröder inclines to the belief that alcoholism sets up some kind of vascular change such that, under conditions of unknown character involving severe brain injury, capillary hemorrhages ensue in various parts of the brain. The region beneath the corpora quadrigemina is for unknown reasons the locus of election for such hemorrhages. It is possible that this tendency is related to the characteristic hemorrhages in anaphylactic intoxication.

Subjects having this symptom complex are often brought to a hospital as cases of delirium tremens. The victims are usually male whisky drinkers of middle age, who have been suffering for months or years from chronic alcoholism. For some days or weeks, headache, pains in various parts of the body, vertigo, and vomiting may precede the ophthalmoplegia. As a rule, the ophthalmoplegia is incidental in a characteristic alcoholic delirium, which otherwise differs from the ordinary delirium tremens in the well-marked mental and bodily weakness of the patient.

The ophthalmoplegia is not absolute nor always an associated palsy. Sometimes the pupil and the levator palpebræ superioris are involved as well. Nystagmus is frequent. Wilbrand and Sänger[1] have pointed out that bilateral ptosis occurs in about one-half the reported cases, although it is not an essential feature. One case in six shows normal vision and unaltered eye grounds. The eye ground changes when found, consist either of a slight neuritis with retinal hemorrhages, or of a pallor of the temporal halves of the papillæ (sign of an alcoholic amblyopia due to chronic neuritis of the papillomacular fiber bundle of the optic nerve.

It is difficult to distinguish the rest of the picture from that in chronic alcoholism. *Muscular weakness,* indistinct *schlaftrunken* (Wernicke) speech, and a *gait* recalling the cerebellar gait are characteristic.

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[1] *Die Neurologie des Auges, Handbuch,* 1900, vol. i.

In the differential diagnosis, brain tumor (especially of the posterior cranial fossa, particularly in the cerebellum) is suggested by the gait and the eye-ground changes. The course of the disease is perhaps more likely to suggest apoplexy or focal encephalomalacia. Not only the gait and the non-febrile course, but also the alterations of consciousness may support such a diagnosis; and, in the light of Schröder's recent histological observations, the disease may perhaps be best regarded as a peculiar kind of apoplectic disease in which multiple minute hemorrhages affect a particular area. The optic neuritis and the symmetry of the ophthalmoplegia eliminate any question of the classical forms of apoplexy. The ocular palsies of botulism (bilateral paralysis or paresis of accommodation, mydriasis, ptosis) present some resemblances to those of Wernicke's disease.

Acute Hemorrhagic Encephalitis, Strümpell Type.—It is probable that many of the cases of acute hemorrhagic encephalitis which Strümpell predicted in 1884 and described in 1890 are of pyogenic origin. Strümpell's first cases showed at autopsy a bilateral bronchopneumonia and a markedly enlarged spleen, in addition to the encephalitis described below. Cultures from the brain lesions proved negative. But Strümpell, after dismissing the hypothesis that his cases belonged to the epidemic meningitis group, assumes that there must be a specific agent for what he conceived was a primary local infection. The possibility of an influenzal origin was not considered by him.

It seems justifiable to put all primary cases of unknown etiology provisionally into this group, which further investigation will undoubtedly resolve. The newer ideas about septicæmia (*e. g.*, in typhoid fever) have so altered our point of view that one naturally hesitates to classify any encephalitis as primary, on the ground that it may result from a blood infection. Since Landsteiner and Popper, and Flexner have successfully transferred anterior poliomyelitis from man to monkeys, there is a possibility that not only anterior poliomyelitis, but also acute encephalitis and Landry's paralysis, may be due either to an ultramicroscopic organism or to protozoa.

Préobrajensky has described the lesions in hemorrhagic encephalitis. In 10 cases isolated foci were found, in 5 other cases multiple foci. The cases with multiple foci were of longer duration. The frontal and occipital lobes are more often attacked than the others. The central ganglion and the temporal lobe are least often injured. No focus was ever observed on the inferior surface of the hemisphere. The cerebellum is more often affected by hemorrhagic encephalitis than by hemorrhage, softening, and syphilis. The foci of encephalitis showed vascular congestion and especially inflammatory changes in the walls of the vessels. Thromboses of the veins are found frequently not only in the brain substance, but also in the meninges, and are more diffuse than the hemorrhagic condition. Valdonio finds inflammatory lesions with thrombi and hemorrhagic lesions and regards the former as primary. He recovered no organisms in two cases.

Orazio D'Allocco has described six cases of acute poliencephalitis in children (one with autopsy). The onset in these cases was sudden, attended with general infectious symptoms. There was a continuous generalized tonic spasm of all the muscles, including those of respiration and of the head, with continual uniform almost rhythmical spasms. The limbs were affected symmetrically, as a rule, but the spasm may be confined to one limb. Spasms are more marked near the head. Muscular excitability is increased.

Anatomically, an endophlebitis and an endarteritis leading to vascular occlusion and degenerative or inflammatory lesions were found.

Acute Bulbar Myelitis (Acute Inferior Poliencephalitis; Acute Inflammatory Bulbar Palsy).—*Acute inferior poliencephalitis* has more verbal than substantial resemblance to *acute superior poliencephalitis,* since the non-inflammatory hemorrhagic character of the latter (Schröder) is replaced in the inferior form by acute inflammatory lesions. These lesions recall closely those of anterior poliomyelitis; in fact, many cases of anterior poliomyelitis show bulbar involvement, so that some writers believe that acute inferior poliencephalitis is a disease closely allied to anterior poliomyelitis—possibly an identical infection with an unusual localization. W. Pasteur's[1] epidemic of seven cases of paralysis occurring in children (ranging from eighteen months to eleven years of age) in one family is often cited in this connection, since some of the cases were cerebral and some spinal. At all events, whether the analogy of anterior poliomyelitis is accepted or the frequent association of bulbar myelitis with influenza epidemics be taken as a hint at the etiology, the disease acute bulbar myelitis is very different from Wernicke's disease both in site and in character. Histologically, there is evidence of acute destruction of nerve tissue, not at all confined to the gray matter, together with vascular congestion and lymphocyte accumulations in the perivascular sheaths. Not only do these lesions affect white matter as well as gray, but the meninges are frequently involved.

The *onset* is rapid, but not apoplectiform. General malaise, headache, vomiting, and sometimes fever precede the local signs of bulbar involvement. The characteristic delirium or sleepiness of Wernicke's disease is not found. As a rule, in from three to seven days there is difficulty in swallowing, with paralysis of the tongue and palate, facial paralysis, and paralysis or paresis of vocal cords.

The *course* depends upon the locus of the inflammatory foci, which may directly involve a greater or smaller number of the gray nuclei (nuclear form of palsy), in which there is least hope of recovery, or may affect the nerves in their intrabulbar course (infranuclear form), in which the prognosis is less grave. On account of the ill-defined limits of the inflammatory process, any given case is somewhat likely at its height to show a combination of nuclear, infranuclear, and even supranuclear involvement. If the subject does not become unconscious in his attack, the course is said to be more favorable. The prognosis is, in general, not so unfavorable as was formerly thought, but death occurs in about one-half the cases. The possible relation of certain cases of recovery to multiple disseminated sclerosis has been mentioned (Oppenheim).

In differential *diagnosis,* syphilis, hemorrhage, and softening of the bulb must be strongly considered, whereas tumor, tubercle, and abscess are less likely to cloud the issue. Syphilis is ordinarily attended by basal meningitic symptoms. Hemorrhage and softening have a sudden or rapid onset which is not characteristic of encephalitis.

Some cases with persistent bulbar phenomena have been attributed to encephalitis; thus, for example, Huet and Lejonne[2] attribute a facial palsy and hemiatrophy of the tongue to the effects of a former acute inferior

[1] *Clin. Soc. Trans.,* London, 1897, xxx, 143.

[2] *Rev. Neurol.,* Paris, 1906, xiv, 105.

poliencephalitis attacking the nuclei of the facialis and hypoglossus of the right side. The onset three years before the time of observation had been with convulsions and fever.

Acute Encephalomyelitis and Poliencephalomyelitis.—These names have sometimes been given to cases of anterior poliomyelitis complicated by lesions higher than the spinal cord; but there are other cases in which the element of anterior poliomyelitis is not so prominent. Possibly cases of Wernicke's disease with a number of hemorrhages below the level of the quadrigemina have yielded so complex a picture as to deserve this name. Cases of acute bulbar myelitis have been not infrequently complicated by lesion higher than the bulb.

A tendency of the symptoms to *descend*, possibly beginning with ophthalmoplegia, going on with bulbar symptoms, and ending with limb disorders, has been noted. There is great irregularity in the degree to which the very various portions of the involved apparatus are diseased. Whereas total ophthalmoplegia and glossopharyngolabial palsy, associated with spinal palsy, are the symptoms of the disease in its full development, yet in cases in which the ophthalmoplegia is complete the bulbar trouble may be limited to slight facial palsy; and in cases in which the glossopharyngolabial palsy is complete there may be no more than ptosis to express the suprabulbar lesion. Oppenheim has endeavored to reduce these diseases to some kind of system, but as yet with little success.

When the cerebral white matter and the included nerve paths are involved, it seems better to name the disease *encephalomyelitis*. The disease has foci as widespread in some instances as to lose its usual purely motor character (Taylor[1] and Oppenheim). These cases vary extremely in outcome, some dying, some recovering, and some remaining with defects. The probable course of several weeks or longer should possibly align them rather with the slower degenerative processes than with acute encephalitis.

General cerebral symptoms are few or confined to the drowsiness and weakness characteristic of Wernicke's disease. Fever sometimes occurs. The facies is said to be characteristic (Hutchinsonian; eyeballs immobile, ptosis, elevated eyebrows), together with relaxation of the lower face, flattening of nasolabial folds, loose-hung limbs.

A case of Combe's[2] illustrates the peculiar combinations of symptoms possible in encephalitis with multiple foci. It is said to have followed influenza. That form of alternate paralysis known as *Weber's syndrome*, viz., right hemiparesis and left ophthalmoplegia, appeared in a boy, aged two years. Weir Mitchell's *posthemiplegic choreiform movements* followed on the right side, but associated with spasmodic movements in the field of the left facial and abducent nerves, amounting to an alternating hemichorea. Later there was weakness of the right oculomotor nerve. Such hemiparesis with crossed paralysis of the oculomotor nerve with tremors of the paralyzed parts corresponds with *Benedikt's syndrome* (due to a lesion of the cerebral peduncle). But the involvement of the left facial and abducent nerves, together with the right-sided hemiparesis, amounts to the *Millard-Gubler syndrome*. The patient, therefore, suffered from a combination of Benedikt's syndrome and the Millard-Gubler syndrome due to a lesion of the pons near the left pyramidal tract (this new syndrome Combe proposes to term the *Inferior Benedikt syndrome*), but in addition showed a complication by incomplete ophthalmoplegia, due to a separate lesion situated in the oculomotor nuclei.

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[1] *Boston Med. and Surg. Jour.*, 1903, cxlviii, 634.

[2] *Syndrome de Benedikt inférieur, Rev. Mens. d. mal. de l'enfance*, 1904, I, xxii, 1.

It is obvious that the diagnosis of such multiple circumscribed lesions and the determination of their encephalitic nature is a matter for the future. At present the general diagnosis must be made largely by elimination of vascular and other focal possibilities and on the ground of the course of the disease. The poliencephalitis here mentioned evidently has considerable alliance with the frankly degenerative diseases of these loci.

It is under this head that much difference of opinion holds concerning distinguishable entities. E. W. Taylor distinguishes the following in this field: Encephalitis, encephalomyelitis, acute ophthalmoplegia, acute superior and inferior poliencephalitis, acute or apoplectiform bulbar myelitis, poliencephalomyelitis, and poliomyelitis.

It may be mentioned at this point that Batten[1] proposes to group anterior poliomyelitis with encephalitis, and neglecting the preëmption of the term "superior poliencephalitis," or Wernicke's disease, Batten classifies as follows: Acute poliencephalitis superior, including cases with frontal, central, occipital, and cerebellar localization; acute poliencephalitis inferior, including cases in which cranial nerve nuclei are affected; acute poliomyelitis anterior. Batten regards both brain and cord disease as due to thrombosis of fine terminal vessels due to an unknown organism or toxin. Batten's classification is of doubtful value, although there are some cases in which there is a thrombosis of the fine terminal vessels (a prominent feature in pneumococcus and streptococcus brain infections demonstrated by Southard and Keene, and Southard and Stratton). It is not proved that thrombosis plays any part in the disease anterior poliomyelitis.

Comby[2] has described an infection of a seven-year-old girl secondary to influenza. The pharynx was the supposed atrium of infection. This case showed phenomena of poliencephalitis, of poliomyelitis, and of polyneuritis. Such occasional instances of generalized intoxication bring out the possible union in a given case of many neurological phenomena, but they do not prove the kind of unity which Batten and Guthrie[3] have asserted.

Alice Hamilton,[4] in 1902, in connection with a case of Patrick's, has discussed the literature of poliencephalomyelitis, and seems to believe in the unity of Wernicke's disease with more diffuse affections, such as bulbar myelitis, encephalomyelitis, and non-hemorrhagic disease. It is doubtful whether the conclusions of Batten and Hamilton as to the unity of all these conditions can be maintained.

Acute Non-suppurative Encephalitis (Acute Hyperplastic Encephalitis, Hayem).—Among non-hemorrhagic forms, Hayem's hyperplastic type is least well recognized and is probably very rare, except in the sense that hyperplastic or proliferative phenomena are the invariable concomitants of all not too severe destructive injuries in the central nervous system.

Encephalitis in the Newborn (Encephalitis Congenita; Encephalitis Interstitialis Congenita; Encephalitis Neonatorum; Stéatose Interstitielle Diffuse de l'Encéphale).[5]—Encephalitis in the newborn occurs at times as the result of septic infection of gastro-intestinal or pulmonary origin (Fischl). A case is on record in which a pathogenic strain of *Staphylococcus pyogenes albus* was grown from the focal lesions (Fischl). Undoubtedly, also, encephalitis may complicate the picture of syphilis in the newborn, although spirochetæ are seldom demonstrable in the nervous system, even in congenital syphilis.

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[1] *Lancet*, 1902, vol. ii.

[2] *Bull. Méd.*, 1906, xx, 41.

[3] *The Clinical Journal*, 1905, p. 176.

[4] *Jour. Med. Research*, 1902, vol. viii.

[5] *Archives de Physiologie*, 1868, vol. i.

Aside from pyogenic, syphilitic, or other recognized forms of encephalitis occurring in the newborn, there is another form, the *encephalitis congenita* of Virchow, which is still *sub judice*. Virchow believed that he had learned the cause of death in a considerable proportion of stillborn and newborn infants, attributing it to encephalitis and myelitis of congenital origin. The only analogies for this form of encephalitis were findings in the brains of children of variolous and syphilitic mothers. For eight or nine years prior to 1865 smallpox raged in Berlin, and there were many stillborn infants, showing little or no sign of gross lesion, but microscopically characteristic foci of fat-laden cells in the white matter. On these changes in the children of variolous mothers Virchow based his claim for a new entity, which he thought would attain much medicolegal importance. In general, he regarded congenital encephalitis as a hitherto unobserved brain disease analogous with the parenchymatous changes of the liver and kidney in the exanthemata.

In histological detail Virchow compared the fat-cell foci—termed by him neuroglia cells undergoing fatty metamorphosis—with precisely similar foci described by him in congenital syphilis (1858) and with the syphilitic hepatic foci of Gubler and interstitial fatty changes in the rare disease known as syphilitic interstitial nephritis. Virchow was also much influenced in his interpretation by his finding of primary interstitial changes in the retina in the amblyopia following Bright's disease.

Hayem, 1868, promplty criticised Virchow's findings, noting the extreme frequency of fat-laden cells in the brains of the newborn. Virchow replied that he considered fat cells of neurogliar origin alone of importance in interstitial encephalitis, and printed a plate from a case of *encephalitis congenita variolosa,* showing great numbers of fatty cells between the vessels.

In the same year Parrot published a piece of work, since largely neglected, on what he termed diffuse interstitial steatosis of the encephalon, and offered clinical histories which proved to Parrot's satisfaction that these changes were due to lack of food. Parrot found similar changes in two starved cats. Parrot's results were reprinted without marked alteration of views in his monograph on athrepsia in 1877.[1]

Jastrowitz regarded the fatty cells figured by Virchow and by Parrot as incidental in the development of the brain. From an extensive material (65 cases), Jastrowitz stated that these cells are found in small numbers in the third month of fetal life, in greater numbers in later months, but as a universal finding in the cerebral white matter only in the newborn. The locus of election for the granule cells is the white matter, and especially the corpus callosum and its processes. The occurrence of groups of granule cells outside these usual loci, *e. g.*, in the gray matter of the cortex or in the basal ganglia, was regarded by Jastrowitz as pathological. The pathological fat-cell groups were thought by Jastrowitz to be due rather to infections and various maternal diseases than to developmental errors or atrophy (Parrot).

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[1] *Clinique des nouveau-nés. L'Athrepsie. Lecons recueillies par le Dr. Troisier,* Paris, 1877.

Virchow,[1] 1883, returned to the discussion with fresh data. He was unable to find the fatty metamorphosis constantly (6 of 9 fetuses, 11 of 27 newborn, 14 of 17 children dying after birth showed the change). Moreover, in the focal form of congenital encephalitis he found evidence of nerve fiber lesions.

Modern opinion inclines to the view that the focal form, in which not only masses of fat-laden cells, but also injury of nerve fibers, can be demonstrated is the true congenital encephalitis. A case of the writer's has shown how streptococci may bring about in the newborn a reaction of the mononuclear cells rather than of the as yet ill-developed polynuclear cells in the meninges. Possibly this finding explains some of the cellular peculiarities of congenital encephalitis.

Giraud[2] concluded from a case of athrepsia with convulsions and other brain symptoms that the disease, contrary to Parrot's opinion, is sometimes curable.

Summary.—There is a form of encephalitis in the newborn which is at times a cause of stillbirth or of death soon after birth, and is due to various factors (sometimes to pyogenic infection, sometimes to syphilis, and sometimes to unknown intoxications), perhaps more often maternal than non-maternal. The disease is histologically characterized by focal lesions of the cerebral white matter (sometimes visible in the gross) showing nerve fiber alterations and accumulations of fat-containing cells. Protracted cases may yield a neurological picture of irregularly distributed convulsions and pareses, respiratory rather than cardiac disorder, and initial, not continued, fever.

Experimental Encephalitis.—The field of experimental encephalitis has not been thoroughly worked. Several men in Ziegler's laboratory have investigated the results of trauma in the brain. Coen[3] demonstrated mitotic figures in the nerve cells surrounding the region of necrosis. Friedmann, in several papers, has described varying phenomena of experimental encephalitis, which in 1904 he summed up by saying that "former distinctions of encephalitis into 'forms' are unnecessary," since sufficiently strong stimuli (meningococcus, influenza bacilli, embolism, aseptic trauma, corrosive substances or heat) can bring about all the different conditions which have been termed encephalitis. In the more severe cases, according to Friedmann, all histological combinations of encephalitic processes may be found ranging from small-cell infiltrations to areas of softening with granule cell deposits and extensive areas of proliferation with giant cells. According to Friedmann, various stages and degrees of these processes have been hemorrhagic, parenchymatous, and hyperplastic encephalitis.

After small traumatic lesions fibrillary sclerosis may follow; after more extensive lesions cellular proliferation is prominent. In cases of hæmatogenous origin, Friedmann emphasizes a primary infection of the small bloodvessels. These have been shown by Southard and Keene, and Southard and Stratton, to characterize pneumococcus and streptococcus infections of the brain. Freidmann, 1904, has given a series of plates illustrating the appearances of encephalitis in rabbits. Koeppen[1] has described one form of end results as a kind of *étât criblé,* in which the fibrillar gliosis has been insufficient to fill the space of the destroyed tissue. In other cases a dense sclerosis follows.

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[1] *Ueber Encephalitis Congenita, Berl. klin. Woch.*, 1883.

[2] *Thèse de Montpellier*, 1906–1907, No. 56.

[3] *Ziegler's Beitr. z. pathol. Anat.*, 1887, Band ii.

Farrar has described the histopathological process in the rabbit's brain after introduction of elder pith. He described a passive period, occupying about twenty-four hours after operation, a proliferative period, and a terminal or involutional period (four weeks). Farrar is inclined to disallow the remarkable phenomena of regeneration described by Borst, in which there was said to be observed a new-growth of medullated fibers into small, celloidin blocks placed in the cortex of the rabbit. The phenomena of pia arachnoiditis in the rabbit after application of glacial acetic acid have been described by FitzGerald.

Experimental work upon bacterial encephalitis as yet scarcely admits systematization. Work upon the peripheral nerve roots and the method of invasion of the central nervous system by bacteria has been done by Homèn and Laitinen, and by Orr and Rows.[2] It is evident from the work of these men that more attention must be paid to the lymphatic route of possible infection. The writer and associated workers have produced experimental brain infections in a variety of ways, using several varieties of pyogenic bacteria. They have produced meningitis, encephalitis, and ependymitis, but so far neither a pure encephalitis nor the important lesions of the small vessels found in many cases of adult encephalitis has been produced in the guinea-pig by these workers. The time relations of the experimental brain infections in the guinea-pig are: *Staphylococcus pyogenes aureus,* intrapulmonary injections, after six hours, focal polynuclear exudation in the meninges; after twelve hours, ependymitis; after twenty-four hours, slight polynuclear leukocytosis in the meninges; after forty-eight hours, subependymal leukocytosis and moderate encephalitis (leukocytes in apposition with nerve cells). After three days meningitis, encephalitis, and ependymitis at their height; after four and five days lymphocytosis and phagocytosis; after six days, phagocytosis for leukocytes; after nine days very slight polynuclear leukocytosis, slight evidence of phagocytosis. After one month the tissues are negative, except for slight fibrillar gliosis, pigment-bearing phagocytes, lymphoid and plasma cells, and eosinophilic polynuclear leukocytes.

In work upon the *pneumococcus,* postorbital inoculations were employed. Many strains of pneumococcus gave no lesion. Polynuclear leukocytosis was noted as early as six hours. The exudate is at its height in three, four, or five days, and is largely confined to the meninges. Some of the strains produced lesions in which mononuclear cells were more prominent than polynuclear cells. Work with the *streptococcus* produced results quite analogous to those with the pneumococcus.

Southard and Richards have investigated guinea-pig brain tissues after postorbital inoculation of *Bacillus typhosus.* In contradistinction to the early crisis of the aureus brain inflammations (three days) and the pneumococcus inflammations (four days), it was found that the *Bacillus typhosus* produced a critical phase from the fifth to the seventh day. Mononuclear elements appear in the pial meshes in the typhosus inoculations by the seventh day. By the tenth day fresh exudative cells have ceased to appear. By the fourteenth day the disease has virtually passed and traces only of the old exudate are found.

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[1] *Arch. f. Psych.,* 1898, Band xxx.

[2] *Brain,* 1904, p. 460; *Review Neurol. Psych.,* 1906, iv, 25; *Brit. Med. Jour.,* 1907, i, 987; *Review Neurol. Psych.,* 1907, v, 345.

It is obvious from these pieces of work that, although Friedmann's account of the non-specificity of various described "forms" of encephalitis is, in general, justifiable, it is probable that variations in the rate as well as in the degree of experimental brain inflammations may be determined, and that further qualitative differences may be expected.

Special work has been done by Cantani on the effect of influenza bacilli on the central nervous system of rabbits. He was able to kill rabbits by brain injection of influenza bacillus in proper amount and of proper virulence. The first symptoms appeared nine to ten hours after injection. Paraplegia of crural type was gradually followed by paralysis of all extremities and convulsions. The autopsies showed evidence of severe intoxication throughout the trunk, as well as meningitis, encephalitis, and ependymitis, with demonstrable influenza bacillus. Injections of killed bacilli into the brain in larger amounts produced the same results. It is possible that the rabbit has a special susceptibility of the brain to the influenza bacillus, such as the spinal cord seems to show to the toxin of the Shiga bacillus.

In connection with experimental encephalitis more work is very desirable in animals. Encephalitis in horses has been long recognized; but it is commonly held that equine encephalitis has a very manifold etiology.

Diagnosis.—The diagnosis of acute encephalitis is not often successfully made, and often not made at all. Perhaps the diagnosis is rendered more accurately in children's clinics than elsewhere, owing to the interest attaching to the Strümpell type. Nevertheless, in the majority of cases the course is either so fulminant or acute as to offer little chance of diagnosis, or else is such as to warrant a diagnosis of "cerebral disease." In a large number of the writer's series of cases of encephalitis and meningo-encephalitis the diagnosis of cerebral disease was made without attempt to differentiate between hemorrhagic encephalitis, massive cerebral hemorrhage, meningitis, and brain syphilis. The attempt of Oppenheim to systematize encephalitis has been so successful that the diagnosis will undoubtedly be rendered more frequently *ante mortem* in the future.

There are few practical difficulties connected with the diagnosis of *hemorrhagic superior poliencephalitis, alcoholic form,* since the history of alcoholism, the acute onset, the associated ocular palsy, the somnolence, delirium, the general weakness (and, as a rule, optic neuritis), stamp the disease. Although Oppenheim has sought to reduce hemorrhagic superior poliencephalitis, alcoholic form; hemorrhagic encephalitis, Strümpell type; and influenzal encephalitis to a single entity on clinical grounds, maintaining that there are intergrading forms uniting all three, yet it does not appear that this position is warranted. Bonhoeffer's original clinical claims and Schröder's recent histological observations go far to show that Wernicke's disease is a rare but perfectly definite disease with definite antecedents and a fairly definite course.

Although Wernicke's disease presents few or no difficulties in diagnosis, the *Strümpell type of acute hemorrhagic encephalitis,* the form termed in this article *pyogenic encephalitis,* and *influenzal encephalitis* give considerable difficulty.

The endeavor should be made in all doubtful acute "cerebral" diseases to establish or eliminate an influenzal origin. Influenzal encephalitis, it must be remembered, occurs *after* rather than during an attack of influenza. Cases occurring in epidemics are more frequently diagnosed than sporadic cases. Lumbar puncture proves of considerable aid. The data of Cohen's recent work on *septicæmic meningitis* must also be considered.[1]

Since many of the cases may turn out to be of pyogenic origin and of pyæmic nature, it is probable that blood cultures will in the future aid extremely in the diagnosis. The etiological data of cultures from lumbar puncture fluid and from the blood will not point unequivocally to encephalitis. On theoretical grounds the positive lumbar puncture culture will point rather to meningitis or to meningo-encephalitis than to a pure encephalitis. Close attention must be paid to all the clinical signs. If we group together influenzal encephalitis, pyogenic encephalitis, and hemorrhagic encephalitis of unknown origin (termed in this article the Strümpell type), the chief conditions to be considered in differential diagnosis are: (1) Other intracranial infective diseases, such as meningococcus meningitis, tuberculous meningitis, pyogenic meningitis, and sinus thrombosis; (2) brain tumor and brain syphilis; (3) cerebral hemorrhage and focal encephalomalacia; (4) certain conditions of cerebral intoxication resembling meningitis but anatomically negative; and (5) rarely acute poisoning, hysteria, and other diseases.

The differential diagnosis in the first group, *intracranial infective diseases,* is greatly aided by lumbar puncture with microscopic examination of the cells in the centrifuge deposit, and with bacteriological examination. This, in doubtful cases, should include an attempt to grow the influenza bacillus on blood media. The finding of blood in the lumbar puncture fluid may suggest chronic internal hemorrhagic pachymeningitis and cerebral hemorrhage as well as acute hemorrhagic encephalitis. Nor will every case of hemorrhagic encephalitis show blood in the cerebrospinal fluid. Blood obtained through technical accident from the vessels at the point of puncture must not be regarded as indicating true intraventricular hemorrhage. A careful cytological examination, preferably by Alzheimer's[2] or some similar method, should be performed. Examinations for the tubercle bacillus or meningococcus and other pyogenic bacteria should be made. A lumbar puncture fluid without leukocytes, blood, or bacteria must not be considered as excluding the possibility of hemorrhagic encephalitis.

Stiff neck, retraction of the abdomen, and hyperæsthesia are not common in encephalitis. Herpes has not been reported. Paralysis of eye muscles is exceptional. Nevertheless, on account of the extensive variation in foci affected by the multiple lesions of hemorrhagic encephalitis, it is improbable that there is any sign of meningitis which may not also occur in some cases of hemorrhagic encephalitis. The diagnosis frequently depends on the association of a monoplegia or hemiplegia with successive involvement of the paralyzed parts or aphasia coming on early in the disease.

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[1] *Annales de l'Institut Pasteur,* 1909.

[2] *Centralbl. f. Nervenheilk.,* 1907, xxx, 499, and Cotton and Ayer, *Review of Neurol. and Psych.,* 1908, vol. vi.

Similar phenomena in meningitis are frequently complications or sequelæ rather than central factors. The acute onset, the drowsiness or tendency to coma, vomiting, convulsions, and optic neuritis offer no points in differential diagnosis against meningitis, nor can much weight be placed upon the condition of the pulse or respiration.

As against *sinus thrombosis* the stasis of blood in the veins of the face has been mentioned by Macewen, but this is not always present. Sinus thrombosis runs a very acute course. The differentiation often fails, except in middle-ear disease.

With respect to the differential diagnosis from *brain tumor*, the onset, the fever, and rapid course are important. Hemorrhagic encephalitis rarely shows an altogether characteristic tumor syndrome. Oppenheim especially warns against the immediate diagnosis of brain tumor in cases showing attacks of cortical epilepsy. Similar remarks apply to brain syphilis when it takes the form of gumma. Brain syphilis in the form of chronic meningitis also runs a quite different course from that of typical hemorrhagic encephalitis. Those rare cases of brain syphilis in which the disease is essentially an encephalitis must give rise to difficulty, except when a history of syphilis can be established. Since these cases occur in secondary syphilis, the differential diagnosis should not prove difficult.

Cerebral hemorrhage and focal encephalomalacia were formerly frequently diagnosed in cases of hemorrhagic encephalitis. In young persons with healthy cardiovascular systems the diagnosis of cerebral hemorrhage or thrombosis may not come into question; but, since hemorrhagic encephalitis occurs in older persons, there is a possibility of confusion. The cases termed by the writer *bacterial apoplexy* occurred in subjects twelve and twenty-two years of age. It is easy to see that in such cases the differential diagnosis between hemorrhagic encephalitis and cerebral hemorrhage would be impossible on theoretical grounds. Practically the paralyses which characterize hemorrhagic encephalitis do not occur simultaneously with the onset of drowsiness or coma. The signs of severe cerebral disease are obvious long before paralyses or convulsions have set in. The paralyses of hemorrhagic encephalitis may increase in intensity from time to time in the course of several hours or a day, presumably owing to the gradual development of inflammatory lesions with oozing of blood. The absence of initial or antecedent fever and of other signs of sepsis will indicate rather a cerebral hemorrhage or focal encephalomalacia due to arterial disease.

Cerebral *intoxication without anatomical signs* (the so-called pseudomeningitis of Krannhals[1]) gives rise to the diagnosis of encephalitis, although more often to the diagnosis of meningitis in some cases. Krannhals' cases occurred in the influenza pandemic of 1889 to 1890. The occurrence of focal symptoms would ordinarily exclude this diagnosis. Poisoning was considered in one of the writer's cases (*Staphylococcus pyogenes aureus*) of bacterial apoplexy, which ran an acute course of three days. Attention to the acute infective feature of encephalitis will usually exclude the diagnosis of *hysteria* with certainty. *Uræmia* and *acetonæmia* may need to be considered.

Encephalitis in Advanced Years.—There is neither predisposition nor lack of predisposition to hemorrhagic encephalitis in old age. The diagnosis as against focal encephalomalacia or cerebral hemorrhage is naturally difficult, especially since febrile conditions (bronchopneumonia) may apparently lend infective features to focal encephalomalacia. Hoppe-Seyler[1] mentions hemorrhagic encephalitis as a rare complication of pneumonia in the aged, and Siemerling, in the same *Lehrbuch*, mentions difficulty in differential diagnosis between sinus thrombosis and encephalitis in the aged. The case of circumscribed hemorrhagic encephalitis reported by Mills, in which there are no data as to etiology, occurred in a woman, aged eighty-three years.

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[1] *Deut. Arch. f. klin. Med.*, 1895, liv, 89.

Encephalitis in Infancy and Childhood.—The possible medicolegal significance of congenital interstitial encephalitis was mentioned by Virchow. Possibly this question should be raised more often in cases of "overlying." Pediatrics practically distinguishes acute encephalitis in infants and a form of encephalitis in older children which shows more tendency to recovery.

Acute and frequently fatal encephalitis of infants is regarded as a primary encephalitis with origin unknown except in certain pyogenic cases. These cases show high fever, stupor or coma, convulsions at the onset as well as later, superficial breathing with occasional Cheyne-Stokes episodes, a rapid, feeble pulse, and sometimes bulging of the fontanelles. The neck and limbs are stiff and flexed. Strabismus sometimes occurs. The occurrence of slight paresis or monospasm of a limb or of the facial nerve is characteristic. The endeavor should be made to determine or eliminate a pyogenic origin. Lumbar puncture findings are helpful as against the diagnosis of meningococcus meningitis.

The encephalitis of older children is often secondary to exanthemata, diphtheria, or pertussis, and has an insidious origin sometimes suggestive of brain tumor. Recovery is the rule in these cases, which sometimes precede the development of frank epilepsy. The child is immobile except for tetanic spasm; the neck is stiff, and opisthotonos may suggest meningitis. Tremor of the limbs, facial palsy, monoplegia, aphasia, convergence or conjugate deviation of the eyes, and optic neuritis may occur. James Taylor[2] has given valuable data, and distinguishes the following varieties of infantile cerebral palsy:

Hemiplegic forms, resulting from encephalitis, vascular lesions and injury.	Acute encephalitis, infantile hemiplegia, infantile monoplegia, idiocy with cranial asymmetry, choreiform hemiparesis, hemiathetosis.
Diplegic forms, resulting from death of cortical cells.	Generalized rigidity, idiocy with general rigidity, paraplegic rigidity, spastic facial diplegia, amaurotic family idiocy, bilateral athetosis, choreiform diplegia, epileptiform myoclonus.

Only the diseases under hemiplegic forms are considered by Taylor to be encephalitic in origin, and of these, infantile (cortical) hemiplegia in the most important. The conditions found, in order of frequency, are acute encephalitis, thrombosis (arterial or venous), hemorrhage, and embolism. The case of Limbeck suggests how porencephaly may be due to encephalitis. Alzheimer has called attention to the relation between idiocy and encephalitis. According to Taylor the victims of infantile hemiplegia are healthy and without hereditary stigmata at onset, and undergo between the ages of one month and six years severe symptoms, consisting of fever, convulsion, and often vomiting and coma. After a period varying from a day to a week the attack becomes less severe, but hemiplegia comes on first in the face, then in the arms, and lastly in the leg. This hemiplegia is flaccid for a few days and afterward spastic. The paralysis clears up to a considerable extent, but, as a rule, not completely. Such are the primary cases. A second group is incidental in certain specific fevers, and probably corresponds to the group of pyogenic encephalitides. Taylor holds that thrombosis is found in certain cases, and calls attention to the possibility of embolism from endocarditis complicating this specific fever.

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[1] *Schwalbe's Lehrbuch der Greisenkrankheiten*, 1909, p. 236.

[2] *Paralysis and Other Diseases of the Nervous System in Childhood and Early Life;* 1905.

Obstetrical injury or other forms of trauma and mechanical rupture of vessels in paroxysms of whooping-cough or in convulsions and meningeal hemorrhage occurring at birth are less important factors. The prenatal cases of infantile hemiplegia are likely to be of thrombotic origin as a result of maternal syphilis. The intrapartum cases are due to obstetrical injury, and the postnatal cases are in general encephalitic.

According to Taylor the following anatomical changes have been found in cases of infantile hemiplegia: Circumscribed atrophic sclerosis (in cases where the nerve elements perish, but the neuroglia survives), cyst formation (in cases where both nerve elements and neuroglia are destroyed), superficial shrunken patches resembling wet wash leather with adjacent atrophic sclerosis (of thrombotic origin), and porencephaly. The neurological phenomena of surviving cases (persistent facial paresis, stunting of growth of arm, choreiform and athetotic movements of arm, characteristic brachial contracture, distortion of bones and joints, posthemiplegic disorders of voluntary and involuntary movements, trophic disturbances and arrest of development, and epileptic attacks) will not be more particularly considered here. About one-half of all cases of infantile hemiplegia are said to be subject to recurrent attacks of epilepsy which begin long after the onset of the hemiplegia.

Treatment.—The febrile nature of hemorrhagic encephalitis indicates certain general measures. Although the hemorrhages are, as a rule, of an oozing character, and the progress of focal symptoms depends rather upon spread of inflammatory lesions than upon massive hemorrhages, it is, nevertheless, desirable to avoid any drug treatment which may stimulate the heart. The patient should rest in bed with the head higher than the trunk, and shielded from light and noise. In the somnolent or comatose condition especial attention must be paid to the administration of food and the evacuation of the bladder and intestine. Incontinence occasionally occurs. Cold compresses or ice bags may be applied to the head. Except in cases of chlorosis, venesection or leeches in the temporal or mastoid region are said to have given good results (Oppenheim). Drug treatment is unsatisfactory. Restless patients may require various narcotics or moist packs. Oppenheim warns against surgical treatment and even against lumbar puncture. It appears that there have been few surgical attempts at alleviation of this disease. It might seem that, were accurate localizing diagnosis possible in certain cases of massive hemorrhage, surgery would be helpful. A case of traumatic subcortical hemorrhage reported by Cushing, 1907, gives a hint in this direction; and cases are undoubtedly seen at autopsy in which evacuation of a clot would have been possible. In general, however, surgeons are doubtful of the value of surgical intervention in encephalitis. Auvray speaks of the difficulties in the differential diagnosis of non-suppurative encephalitis and brain abscess, but would not intervene in encephalitis. Operation in meningo-encephalitis (Macewen's case) has been done, and Oppenheim calls attention to Hahn's case (1896), in which trephining was performed under the false impression that abscess or hemorrhage of traumatic origin was present.

Since in the future our diagnoses of encephalitis must improve in the line of etiology, it is possible that especially in the influenzal and pyogenic groups the possibilities of immunization and opsonic treatment may be exploited. The somewhat rare chance of a syphilitic encephalitis must be considered.

BRAIN ABSCESS.

Brain abscess is a focal destructive disease of brain tissues, characterized by the presence of pus, and is ordinarily distinguished from tubercle, gumma, neoplasm, and cyst of softening, despite the fact that cavities with puriform contents may be found in these conditions. As in the rest of the body, artificial aseptic abscesses can be produced by chemical or physical means within the cranium. Non-experimental abscesses are now generally stated to be invariably due to microörganisms. It is useful to bear in mind, however, that even in man a variety of destructive aseptic lesions can be produced by violence from falls or blows, and that only months or years later these quiescent lesions may be occupied by bacteria. Recent knowledge concerning the frequency of bacteriæmia giving no clinical sign has explained the otherwise mysterious occurrence of latent traumatic abscess.

History and Sources.—References, both monographic and periodical, to the subject of brain abscess are very scattering before 1850. Thereafter the work of the otologist Toynbee,[1] of Lebert,[2] of Biermer (particularly contained in R. Meyer's dissertation,[3] 1867), excited interest which was brought to a focus in Huguenin's systematic work of 1876.[4] Surgical interest arose which culminated in the classical work of Macewen (1893). The otological development was maintained by Körner[5] in various publications. The best systematic treatise since Huguenin is by Oppenheim in Nothnagel's *System*, 1897, greatly developed in a second edition of over 300 pages by Oppenheim and Cassirer,[6] 1909. The most striking recent observations are derived from otology, especially from the diagnostic point of view. The bacteriology of brain abscess remains a comparatively neglected field, and most writers feel that cases cannot be clinically differentiated according to microörganisms.

[1] *Med. Chir. Trans.*, London, 1851, xxxiv, 239.

[2] *Virch. Arch. f. path. Anat., etc.*, 1856, x, 78, 352, 426.

[3] *Zur Pathologie des Hirnabscesses*, 1867.

[4] *Von Ziemssen's Handbuch d. spec. Path. u. Therapie*, 1876, Band ii.

[5] *Die Otitischen Erkrankungen des Hirns*, 1902; *Nachträge*, 1908.

[6] *Der Hirnabszess*, 1909.

Etiology.—A great variety of organisms has been demonstrated in brain abscess, not all of which are surely concerned in the original production of the lesion, but may settle in preëxistent lesions. Malinowski, 1891, showed that suppurative processes could sometimes be induced in the normal brain of the dog by injections of pyogens, but constantly in brains that had been injured ten days previously.

Pathology and Pathogenesis.—Abscesses of the brain occur in all sizes from approximately half the size of a hemisphere down to the barely visible. The smallest abscesses are, as a rule, pyæmic in origin and multiple; they intergrade with encephalitis, the non-suppurative form of which may be so named merely because no pus is visible, whereas, polynuclear leukocytes may be easily demonstrable microscopically. Nevertheless, there is good reason to distinguish such interstitial inflammatory conditions from frank abscess, as in other organs and tissues. The larger abscesses are usually single and are frequently objects of surprise at autopsy, because the volume of "silent" brain tissue and the chance of physiological compensation for destroyed mechanisms are not precisely remembered by the anatomist. The larger single abscesses are apt to be subcortical rather than cortical, and are likely to break through to the surface or into the ventricles late in the disease.

The pathogenesis is by extension from external infected wounds (acute traumatic abscess), by extension from sinus thrombosis, by extension through diseased bone or by lymphatic paths (otitic, rhinogenic, orbital), by blood infection (pyæmic abscesses, abscesses metastatic from bronchiectasis, empyema). The pathogenesis of latent brain abscess is dubious, although there can be no doubt of the part played by blood-borne infection. Occasionally there is an actual demonstration of pigment derived from lung lesions in the metastatic cases.

The abscesses contain, as a rule, a green or yellowish-green, or yellowish pus, generally watery, and in long-standing cases sometimes almost clear. The abscess wall after some days (five or six, according to Friedmann's experimental data, eight or ten days in man) begins to show a membrane. This membrane shows a large amount of collagenous tissue, intermingled with neuroglia in the outer zones. The development of mesodermal reaction in these abscesses is greater than in most other intraneuraxial lesions (solitary tubercle excepted), but for all that there is no tendency to obliteration of the cavity. Such obliteration must be the rarest of events. The investing membrane may be so dense and coherent that the whole abscess may be stripped out, especially from a brain somewhat softened by postmortem change. Frequently death, from rupture into the ventricles with generalized pressure symptoms or rupture into the meninges with a terminal leptomeningitis, intervenes before such membrane formation.

Symptoms.—The general symptoms are those of heightened intracranial pressure, and in the main resemble those of brain tumor. Deep-lying abscesses tend to heighten intracranial pressure more than superficial abscesses. Subtentorial abscesses produce a general heightening of pressure by means of hydrocephalus. The general symptoms to be considered are:

1. *Headache.* It is rare for a case of brain abscess to run a complete course without headache. Even in the latent period of chronic abscess headache may occur periodically. The onset of fever, attacks of coughing and sneezing, the use of alcohol and coffee are likely to increase the pain.

The headache is apt to be of the dull, bursting type, and is inclined to localize itself upon the side of the abscess. Cerebellar abscesses yield, as a rule, a regionary headache, but there is a surprising number of cerebellar cases with frontal headache. A certain number of cases, perhaps the majority, show localized sensitiveness upon pressure or percussion over the seat of the abscess. During the period of encapsulation the headache of abscess is perhaps less severe than that of tumor; but rapidly spreading abscesses yield headaches of maximal intensity.

2. *Vomiting.* Vomiting occurs in practically all cases, as a rule at the time when headache is most marked, certainly without relation to the condition of the stomach, and often apparently excited by a change of position. Subtentorial abscesses are perhaps more prone to show this symptom.

3. *Vertigo.* Vertigo, unlike headache and vomiting, is inconstant in brain abscess, and perhaps characterizes only a minority of cases. Moreover, since the majority of cases with abscess symptoms give at least a suspicion of being otitic in origin, the vertigo runs a chance of confusion with aural phenomena.

4. *Slowing of Pulse.* At the height of the disease the pulse is usually subnormal (perhaps 50 to 56). Pulse rates of 40 and 30 occur, and rarely it may diminish to 10. A slow pulse is especially helpful in the differentiation of brain abscess and local ear disease and sinus thrombosis.

5. *Respiratory disorder,* usually with tendency to slowing, is not infrequent, particularly in cerebellar abscesses.

6. *Eye-ground Changes.* These are less common and severe in brain abscess than in tumor. They are found, as a rule, when the other symptoms of brain abscess are pronounced.

Generalized convulsions occur in a minority of the cases. Cerebral abscesses in children appear to cause convulsions more often than brain abscesses in adults. Late in the disease and in cases in which the pus bursts into the ventricles convulsions are more common.

Hebetude, sleepiness, indolence, and an appearance of fatigue are characteristic. Absolute coma occurs late and may occur repeatedly in a given case. Episodic attacks of restlessness, confusion, or excitement may set in at any time, and are characteristic of the initial stage in cases having an acute onset. They are apt to accompany attacks of fever. Cases suggestive of the psychiatric diagnosis of delirium are rare. The latent cases may suggest melancholia.

Temperature.—Normal temperature may persist throughout, and periods of subnormal temperature characterize some cases. The initial stages of cases having acute onset usually exhibit fever. As Oppenheim suggests, the insidious onset of many cases and the subsidence of fever before the physician is called in many others have led to the idea that brain abscess is characteristically non-febrile. Naturally the ventricular and meningeal complications of the terminal stages may lead to fever. Macewen's data show that the majority of cases throughout observation show normal or subnormal temperatures. Perhaps the latent encapsulated abscesses of a chronic type are those which most characteristically fail to show fever. Certainly a persistent high temperature or a typically intermittent fever is not characteristic of uncomplicated brain abscess, that is, abscess without meningitis or otitis.

Focal Symptoms.—Although cases of brain abscess sometimes fail to yield focal symptoms, yet the majority yield fairly characteristic symptoms which often betray the true nature and origin of the lesions. Thus the occurrence of motor symptoms is most characteristic in traumatic and metastatic abscesses; whereas frontal abscesses are characteristically rhinogenic; temporal and cerebellar, otogenic. A few metastatic and traumatic abscesses have been found localized in the occipital region. Abscesses of the pons, the medulla, and the brachium conjunctivum are decidedly uncommon. Local variations in the relatively normal tissue surrounding abscesses are commonly stated to account for rapid modifications in the symptom picture, and for the immediate diminution in symptoms following surgical drainage of abscess cavities.

1. *Focal Motor Symptoms.* These are: (*a*) *Epileptic symptoms* of the Jacksonian type whose distribution may easily serve to indicate the spread of the abscess. These convulsive phenomena naturally occur more often with the cortical than with deeper lesions. The possibility is always to be borne in mind that the convulsions are due not to destructive cortical lesions, but to encephalitic or meningitic changes overlying abscess. (*b*) *Paralytic symptoms* tend to be monoplegic, and, if hemiplegia eventuates, the parts are successively and not simultaneously involved. *Disorders of sensation* are often masked by the patient's mental state.

2. *Frontal Symptoms.* These are frequently absent or hard to differentiate. The vicinity of the motor zone permits, in the midst of indeterminate symptoms, the development in later stages of brachial or facial symptoms. Conjugate deviation of head and eyes toward the side of lesion has been noted in connection with epileptic attacks. The mental symptoms which one might expect and which occasionally arise in the brain tumors so localized have generally failed of demonstration.

3. *Temporal Symptoms.* Temporal abscess is practically never found unexpectedly at autopsy in clinical cases properly observed. The data concerning contralateral and homolateral disturbances of hearing are still equivocal, both on account of the sensorial state of the patient and on account of the frequent involvement of the peripheral auditory apparatus in these cases. Aphasic symptoms are characteristic in left-sided lesions. The sensory aphasia of Wernicke, as Wernicke himself pointed out, does not ordinarily develop from the temporal lobe abscess as it usually occurs, since the cortex and white matter of the superior temporal gyrus are not usually involved until late. Oppenheim has pointed out that the lesion characteristically cuts the association paths rather than the auditory centres themselves, so that an amnestic aphasia supervenes in which the patient speaks little and has lost command of many words. The understanding of terms for simple things remains intact. Slight paraphasia and inability to name objects, with maintenance of power to repeat words, are shown. The abscess may disconnect the auditory and the optic centres and thereby effect a partial word-deafness with maintenance of the understanding of words without visual content. Hemianopsia may be produced by deeper lesions. Contralateral motor phenomena are paralytic rather than epileptic in character, and are probably best regarded as due to involvement of the internal capsule. Muscular rigidity, increased deep reflexes, diminution in the abdominal reflexes, development of the Babinski reflex occur. Macewen and Körner have pointed out that oculomotor palsy is frequently

found on the side of the lesion. Oculomotor palsy and contralateral facial and brachial monoplegia, with other abscess symptoms, point to temporal localization.

4. *Cerebellar Symptoms.* The most important cerebellar symptoms cannot be precisely spoken of as focal; but cerebellar ataxia, Babinski's cerebellar asynergy, general muscular weakness, occasionally hemiataxia, Babinski's adiadochokinesis, forced movements, peculiar attitudes of head and body, vertigo and vomiting, nystagmus, convulsions, and various effects of compression of lower structures may be found. Pain in the back of the head and nuchal region, retraction of the head, and stiff neck are more characteristic of cerebellar abscess than of other types.

5. *Occipital Symptoms.* Beyond hemianopsia and possibly word-blindness there are few characteristic symptoms from occipital abscess.

Further localizing points are mentioned under the diagnosis of abscesses classified below as of various origin: (1) Traumatic. (2) Otitic. (3) Metastatic. (4) Rhinogenic. (5) The so-called idiopathic brain abscess.

Diagnosis.—Traumatic Brain Abscess.—Traumatic brain abscesses form about one-quarter of reported cases (Church and Peterson). They are likely to be superficial and situated directly below the locus of trauma, and naturally affect the convexity, particularly the frontal and parietal regions, more often than other parts of the brain. In contradistinction to localized traumatic leptomeningitis, which may develop very shortly after the trauma, traumatic brain abscess begins to show symptoms only after several days (*acute traumatic brain abscess*) or after a long latent period of weeks to years (*latent traumatic brain abscess*).

In the *acute traumatic form,* the interval between injury and development of frank *symptoms of abscess* may be occupied by signs of brain laceration or by certain meningeal symptoms, followed by a somewhat sudden development (several days to two weeks after trauma) of the signs of heightened brain pressure with fever. Whereupon, with the development of focal signs, the picture of abscess becomes complete. Involvement of motor parts of the brain is obviously more often the rule in traumatic than in other forms of brain abscess, so that both the history of trauma, with local appearances, and the course of the disease, with its focal signs, somewhat simplify the diagnosis. Nevertheless, it may not be easy to tell such cases from cases of suppurative meningitis. It is said that muscular hypertonus and generalized hyperæsthesia are less apt to develop in abscess cases. The cortical epilepsy or monoplegic symptoms, which are not infrequent in encephalitis or with cortical cysts of softening, sometimes occur in traumatic brain abscess, but speedily develop into hemiparesis or hemiplegia, possibly with aphasia. Sometimes the hemiplegia comes on suddenly. Again, there are rather characteristic short remissions which indicate that the process of abscess development is by no means so free as that of a meningitis of similar localization. Oppenheim states that the focal signs of brain abscess are less likely to be masked by general signs than are the focal signs of meningitis, an observation which probably signifies that abscess may proceed for many hours or days without interfering with intracranial pressure. The fever which may characterize the initial onset of pressure symptoms need not be a prominent feature in the later course. In fact, absence of fever as well as slow pulse are commonly thought to favor the diagnosis of abscess when the symptoms of the disease are fully developed. The frequent co-existence of abscess and localized meningitis, as emphasized by Huguenin, must not be forgotten in the analysis of symptoms. In the absence of surgical interference, death may ensue within three weeks.

In the *latent traumatic form* we find a similar preference for frontal, central, or parietal localization, but, although these latent abscesses are certainly related to overlying local trauma, yet they are not due, in the opinion of most writers, to direct infection from superficial injured tissues. Possibly subinfection with organisms, circulating in the blood but derived from some quite different source, may account for the lighting up of an acute inflammation in the mechanically injured brain tissue. These foci would otherwise, and doubtless often do, gradually heal and in the end produce quite imperceptible functional changes. A careful inspection of the latent periods in such cases may often reveal suggestive symptoms, as a rule, of an irritative or "functional" character. The frank onset of the disease is attended with headache, perhaps localized and accompanied by pain on percussion of the adjacent bone. Vomiting, vertigo, tremors, slow pulse, are characteristic, and a large number of cases fail to show fever, but may even exhibit a subnormal temperature. Such abscesses are consistent with but slight alterations of consciousness, but investigation usually discovers some change, if nothing more than unusual somnolence; such changes when observed are often variable. Changes in the eye-grounds are not constant. Emaciation and gastro-intestinal disorders are frequent. There is great possibility of confusing such latent abscesses with brain tumor; in the differential diagnosis we are aided by the occasional febrile attacks, the rapid progression, and the lack or late development of eye-ground changes in abscess.

A recent instance of blood-borne infection of intracranial abscess with Bacillus typhosus in a traumatic case under treatment for typhoid fever has been reported by Gurd and Welles.[1]

Otitic Brain Abscess.—One-third to one-half of all cases of brain abscess are said to follow purulent otitis media. Of course, only a small proportion of such otitides give rise to brain abscess, and then often many years after the onset. Mastoiditis, temporal bone disease, and the so-called cholesteatoma (of the otologists), and cases of otitis media which do not secure free drainage (either naturally or surgically) are especially dangerous. Less frequently brain abscess follows immediately upon an acute otitis media. A somewhat rare complication is brain abscess ensuing upon the temporal bone disease found in diabetes. Otitic abscesses of the brain are rare in cases which have never undergone perforation.

Like the traumatic forms, otitic brain abscess is usually solitary. Its characteristic locus is the temporal lobe, and if in the right temporal lobe it may yield no localizing sign, but if in the left, may yield word deafness or sensory aphasia, permitting accurate local diagnosis. Naturally, the general symptoms may hinder the detection of this feature. Let such an abscess spread inward, and a spastic hemiparesis, possibly associated with hemianæsthesia and hemianopsia, will ensue, as a result of pressure upon, or destruction of, the underlying white paths. Oculomotor and abducent disorders, especially ptosis, may be associated with the other symptoms through pressure upon the corresponding nerves.

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[1] *Annals of Surgery*, 1908, xlvii, 4 to 9.

Temporal lobe abscess is about twice as frequent as cerebellar abscess following ear disease (Heimann,[1] 428 temporal, 198 cerebellar; Neumann,[2] 336 temporal, 196 cerebellar). Cerebellar otitic abscesses in about nine cases out of ten (Neumann) produce symptoms. One group of symptoms (*vestibular nystagmus, vertigo,* and *vestibular ataxia*) is dependent upon involvement of Deiters' nucleus. Inasmuch as labyrinthitis and cerebellar abscess often co-exist, the diagnosis of vestibular nystagmus may be difficult. The ataxia of cerebellar otitic abscess is, according to Bárány, a characteristic compound of vestibular and cerebellar features. Peculiar correlations between the direction of nystagmus, the position of the head and trunk, and distribution of ataxia have been described by the otologists. Nystagmus to the diseased side, described as Neumann's sign, has been confirmed in three of five cases of cerebellar abscess by Hegener. Another group of symptoms (hemiparesis and hemiataxia) depends upon interruption of white paths in the cerebellar tissue. Rapid emaciation and anæmia have characterized many cases (Okada). Uncomplicated cases are apt to run an afebrile course. A slow pulse, without correspondence with such fever as may occur, as in other processes, shows heightened intracranial pressure. Occipital pain is *not* especially characteristic of cerebellar abscess; on the contrary, frontal pain is not infrequent (spread of irritation from a recurrent branch of the ophthalmic division of the trigeminal nerve, supplying the tentorium, to other branches of that division, Krause).

Temporal lobe abscess and cerebellar abscess are often difficult to distinguish. Hemianopsia is uncommon in cerebellar abscess. The speech disturbances of cerebellar abscess are rather bulbar than cerebral in character. The hemiparesis of cerebellar abscess is homolateral; of temporal abscess, contralateral. Palsies of isolated eye muscles are the rule in cerebellar abscess, whereas ptosis, external strabismus, and oculomotor palsy characterize the temporal cases. The pain of temporal lobe abscess cases is temporal or parietal, as against the occipital or frontal pain of cerebellar abscess. Nystagmus, stiff neck, and sensitiveness of neck tissues are characteristic of cerebellar cases.

The law of Toynbee, according to which disease of the tympanic cavity gave rise to cerebral abscess, whereas disease of the external meatus threatened rather the lateral sinus and the cerebellum, and labyrinthine disease was likely to lead to bulbar involvement, has been much modified by more recent knowledge as to possible paths of infection. Huguenin, for instance, pointed out that the cerebellum could be involved directly along the facial and auditory nerves.

Cases of Stokes, of Habermann, and of Bloch and Hechinger indicate that the sense of smell should be tested in this group of cases. Twice the anosmia was homolateral with abscess, once contralateral. Dench[3] has published an analysis of 102 recorded cases of cerebellar abscess (33 recoveries) and 100 cases of cerebral abscess (52 recoveries) of otitic origin.

Metastatic Brain Abscess.—The diagnosis of metastatic brain abscess (about 10 per cent. of all cases, Gowers) must take into account the predominant sources for embolism. Bronchiectatic abscesses, pulmonary gangrene, lung abscess, pleural empyema, ulcerative endocarditis, pyæmic

[1] *Arch. f. Ohrenh.*, 1905, lxvi, 67.

[2] *Der otitische Kleinhirnabszess*, 1907.

[3] Otitic Brain Abscess, *Amer. Jour. Med. Sci.*, 1907, cxxxiv, p. 692.

processes of very various origin, often permit the production of brain abscesses, and, as in other hæmatogenous brain diseases, the territory of the Sylvian arteries is especially prone to involvement. It is also stated that the left Sylvian region is the locus of election for metastatic abscess. Metastatic brain abscess is more often multiple than single and the symptoms more closely resemble those of the acute traumatic form than those of otitic abscesses. Embolic in origin, this disease is apt to have an apoplectiform onset, but the effects of the septic emboli are likely to continue and create sudden fresh attacks, due either to extension of local processes or to the accession of more emboli. The emboli are usually small and carried to the small branches supplying the cortex cerebri or its subjacent white matter.

The Sylvian predilection of such emboli secures a predominantly motor set of symptoms for these cases. But in some instances the foci are so many that localization is impossible. Eye-ground changes usually fail to develop in the acute course of these cases, nor are vomiting and vertigo such prominent symptoms as in most other forms of brain abscess.

Rhinogenic Brain Abscess.—Gerber[1] has collected from the literature 66 cases of brain abscess following frontal sinus disease. In the majority of cases the posterior wall of the sinus was diseased, and the abscesses are usually found involving the gyri of the orbital surface, and vary in size up to that of an orange. The characteristic absence of focal symptoms, the occurrence of frontal sinus symptoms, and the complicating presence of meningitis symptoms render the diagnosis difficult. Eye-ground changes are not uncommon, so that a diagnosis as against brain tumor has to be guarded. If, after frontal sinus operation, the headaches continue or increase, and fever, loss of appetite, alteration of general attitude, slowness of speech, restlessness alternating with apathy set in, orbital brain abscess may be suspected (Gerber). Later, several of the general symptoms of brain abscess may set in.

Idiopathic Brain Abscess.—Huguenin was forced to the opinion that idiopathic suppuration of the brain does not exist. Gowers states that in about one-sixth of the total number of cases no cause for the abscess can be discovered. He believes that forgotten trauma is an important feature of some of these cases, but regards the whole matter as an open question. Oppenheim also suggests forgotten trauma, and thinks that infectious diseases may at times produce suppurative disease in the brain without foci elsewhere (possibly through an otitis?).

Course and General Diagnostic Features.—The symptoms of brain abscess may all occur separately with meningitis, sinus thrombosis, and brain tumor, especially if these be complicated by extension of purulent or destructive processes. Moreover, syphilis sometimes yields a similar picture, and the difficult differentiation of symptoms of labyrinthine and central origin may often leave the nature of a case in doubt. In the absence of ear disease, disease of the nose and its communicating sinuses, bronchiectasis, empyema, or other peripheral source of metastasis, the chances are against the diagnosis of brain abscess. The history of trauma is unfortunately often dubious of interpretation.

As against *meningitis*, abscess more often produces hemiplegia, monoplegia, or aphasia, whereas irritative symptoms are more common in meningitis. Cerebellar abscess, however, may produce the same retraction of the head and stiffness of the neck as meningitis. The absence of fever speaks against meningitis. The presence of fever favors neither diagnosis.

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[1] *Beitr. zur Anat. Path. und Klinik der Stirnhöhlen*, 1909.

As against *sinus thrombosis*, the lack of high fever, of rapid pulse, and of tenderness and swelling over the internal jugular vein at its origin may be decisive for abscess. The occasional co-existence of the two lesions must be remembered. As against *brain tumor*, double optic neuritis is less frequent in abscess. Bramwell states that he never commits himself to a positive diagnosis of intracranial tumor unless suppurative ear and nose disease can be excluded.

In the majority of cases three or four stages may be distinguished: (1) The initial stage (lasting a day to a week), characterized by headache, vomiting, slow cerebration, confusion, delirium, fever, and rapid or slow pulse, with possibly stiffness of the neck, pupillary differences, convulsive phenomena, and the relative *absence* of focal symptoms. (2) The latent period (lasting weeks, months, or years, on the average one to three months), either absolute, when the symptoms are completely lacking, or relative, characterized perhaps by episodes of headache, vomiting, vertigo, and convulsions, and failing to show any constant phenomena save, possibly, depression. (3) The stage of abscess symptoms properly speaking (lasting some days or weeks), characterized by the signs of heightened intracranial pressure and the extension of suppuration. (4) The terminal stage.

Prognosis and Treatment.—Left to itself, brain abscess kills, despite the extraordinary periods of latency often reported. It may kill through heightening of intracranial pressure, perhaps effected by spreading of suppuration into the ventricles or the meninges. The treatment is essentially surgical, and Oppenheim remarks how unfavorable seemed the surgical results as depicted by Huguenin in 1876, and how relatively favorable as shown by Wernicke in 1881.

The excellence and extent of modern otological work should decrease the number of cases of brain abscess of the temporal and cerebellar type. Oppenheim counsels opening the skull and searching for suppuration in all cases in which the diagnosis of traumatic brain abscess is certain or even probable. The indications for operation in otitic cases are scarcely less decisive. Investigation of the cerebral and cerebellar conditions in the course of otological operations must be left to the judgment of the otologist or surgeon. Every large clinic has cases in which an abscess cavity in these regions has been "just missed"by the operator. Oppenheim goes so far as to state that purulent pachymeningitis, sinus thrombosis, or even beginning pyæmia do not contra-indicate operation. The onset of coma does not prove that surgery would fail. Obviously operations upon metastatic abscesses are less likely to prolong life, and multiple pyæmic abscesses are beyond our present range of treatment.

The mechanical increase of intracranial pressure either directly or through the effects of drugs or foodstuffs upon the vascular system should be avoided. Therapeutic measures against headache (narcotics, morphine, ice bags) and attention to the possibility of bedsores and the condition of the bladder and rectum, to say nothing of general nursing and hygienic measures, are obvious indications.

XXII

A STUDY OF ERRORS IN THE DIAGNOSIS OF GENERAL PARESIS[1]

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Diagnosis of General Paresis

Two hundred and forty-seven cases of insanity were observed in the Danvers daily clinics and later autopsied in the pathological laboratory during the years 1904 to 1908 inclusive. 61 of these 247 cases, namely 25 per cent. were diagnosed with more or less certainty as cases of general paresis. 41 of these 61 cases were regarded as *clinically certain,* since every one present at the clinic committed himself to the diagnosis. 7 of the cases may be regarded as *clinically probable,* since the majority of

Diagnosis of General Paresis

Clinically certain	41
Verified post mortem	35
Clinically probable	7
Verified post mortem	2
Clinically dubious	13
Found post mortem	6
Unexpectedly found post mortem (in series of 186)	2
Clinical total	61
Histopathological total	2 plus 43

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[1] Read at the thirty-fifth annual meeting of the American Neurological Association, May 27, 28 and 29, 1909.

staff members favored the diagnosis. 13 cases are classified as clinically dubious, since, although the diagnosis of general paresis was prominently considered, other diagnoses were also possible. The clinically dubious group includes also cases in which diagnostic doubt was expressed by several staff members.

The table displays these cases of clinical general paresis together with the true diagnoses based on post mortem evidence. The table also includes two cases of general paresis unexpectedly found post mortem in the residue of 186 cases of this series (247 less 61 paretic).

Seventy per cent. of the cases in which general paresis was certain, probable, or even prominently considered, proved histopathologically cases of general paresis. Less than 1 per cent. of a series of 186 cases in which the diagnosis of general paresis was not considered, proved to be instances of general paresis.

It is clear that the errors in diagnosis found in the *clinically certain* group are of the first importance in our diagnostic study. 85 per cent of these cases obtained the correct diagnosis at staff meeting. What is the cause of incorrect diagnosis in the remaining 15 per cent.? There were six of such cases, and it seems worth while to present abstracts of the clinical histories and autopsy protocols in these cases.

The first wrongly diagnosed case was that of E. C., D. I. H. 11987, Path. Lab. 893, and has been amply described by Prof. A. M. Barrett as a case of *severe progressive arteriosclerotic brain atrophy with tabes-like complications* in his "Study of Mental Diseases Associated with Cerebral Arteriosclerosis," *Am. Jour. Insanity,* LXII, 1, 1905, pp. 48–50. The confusing feature from the standpoint of diagnosis was the tabes-like picture; and histopathologically there proved to be, in addition to bilateral pyramidal tract disease, a lumbosacral tabes or tabetiform disease.

The error in diagnosis in the second case, H. F., D. I. H., 11994, Path. Lab. 1118, is possibly attributable to complicating cerebellar and spinal cord disease. The diagnostic sheet reads: "General paralysis, made from characteristic signs, absent reflexes, speech defect, and general deterioration." The case seems worth presenting in detail.

H. F., male, gear maker, born 1850.

Heredity.—Maternal grandmother insane. Mother insane at 52, became demented and lost use of limbs, died at 71. Aunt insane.

Personal History.—Common school education. Capable workman till within a few months. Early in life alcoholic. Drunk almost every week until 1899 or 1900. Irritable, nervous, selfish, loose in relations with women. Venereal disease denied by wife. Married 1883. Three frail children. No miscarriages. Neuralgia in 1901 or 1902.

January, 1904, patient left carriage shop on account of mistakes in work, became more pleasant, childish, fearful, talkative, did funny things, later became vagrant, stole from fruit stores, smoked cigarettes picked up in street, and became restless and irritable.

Committed to D. I. H., June 24, 1904, with slightly enlarged heart, somewhat heightened blood pressure, and a slight sediment of epithelial cells in urine.

Romberg's sign was present, but there was little or no demonstrable incoördination otherwise. Very slight tremor of fingers. Left knee jerk absent, right obtained on reënforcement. Achilles jerks absent. Triceps, wrist and normal plantar reflexes present. Pupils reacted to accommodation but very slightly, if at all, to light. Sensations normal except in legs. The legs show preservation of tactile and temperature senses, but abolition of pain sense except over dorsum of foot.

Speech showed slurring of syllables and " brigrade " for " brigade." Disorientation for time, place and in part for persons. Admitted that his work had been deficient, but regarded himself as well. Emotionally variable, crying at times and suddenly becoming jocular.

Eloped July 3 and somehow reached his wife's house in a neighboring city.

Euphoria persisted. The pupils continued Argyll-Robertson, and the knee jerks remained absent. Became oriented for place and partially as to time (month and day of week correct).

During 1905 failure became rapid with ataxia of legs, persistent euphoria, and loss of weight.

Convulsions, regarded as general paretic, developed in 1906. Death sudden December 7, 1906.

Post Mortem Findings.—The *cause of death* was streptococcus septicemia, probably derived from a gangrenous bronchopneumonia or related with a small thrombus of the right auricular appendix. There was also an acute purulent otitis media, mastoiditis and sphenoidal sinusitis, as well as extensive decubitus. From this decubitus or from the intestinal tract may have been derived the numerous colonies of *Bacillus coli communis* which developed on plates from the cerebrospinal fluid.

Arteriosclerosis was little in evidence, being confined to the coronary, right vertebral and carotid arteries (slight in all). Cysts of softening existed in the posterior part of each dentate nucleus and may probably be interpreted as indicating vascular disease.

Chronic disease outside the nervous system was prominent and in part suggestive of senile findings: milk patches of pericardium, adhesions about liver and gall-bladder, adhesions about spleen, adhesions and fibrous thickening of parietal peritoneum, adhesions in both pleural cavities, chronic diffuse nephritis, hypertrophy of bladder wall, dense calvarium, dural adhesions.

The *nervous system* showed several unexpected features. The *absence of chronic leptomeningitis* was striking: the pia mater was everywhere delicate and transparent except that the walls of the cerebellar and chiasmal cisternæ were thickened and that there were slight opacities along the sulcal veins of the convexity. Brain weight 1,090 grams. There was a generalized *sclerosis and pigmentation of the cerebral cortex*. The sclerosis varied in degree and was most marked in the prefrontal regions, the anterior halves of the superior frontal gyri, the middle third of the right precentral gyrus, the region of the splenium on the left side, and the sagittal rami. If the *Bacillus coli communis* found in the cerebrospinal fluid had any effect upon the consistence of the brain, obviously hard to prove in a brain of leathery consistence at the outset, it was shown only in the right Rolandic area in the vicinity of the sclerotic part of the precentral gyrus. *Granular ependymitis* of all ventricles. Weight of cerebellum, pons and bulb 135 grams. Perhaps the most remarkable feature of all in the case was the occurrence of *cysts of softening* in the posterior part of each *dentate nucleus*.

The third case of diagnostic error was that of C. D., D. I. H. 12,263, Path. Lab. 924.

Heredity.—Mother dead of phthisis at 63. Two sisters and three brothers living and normal. One brother dead of mastoid abscess. One sister recovered from "nervous prostration"; one sister "peculiar."

Personal History.—Born 1849. Education limited. Calculating ability always good. Occupation at first hostler, later assistant with wholesale drug company for 32 years. Tobacco in excess till 1901. Moderate constant use of alcohol till 1899. "Nervous prostration" (seclusive, "head troubled him") about 1894. Otitis media (delirium, swelling of feet, "rheumatism") in 1898. Since this attack of otitis media "not altogether right," "a little off in his talk at times." In 1902 patient quarreled with his employer and left work. Since then has traded in hens and pigs, has done "peculiar" things, has become forgetful especially of recent events. Married in 1872. (Miscarriages of unknown cause.) Venereal disease denied. No children.

In 1904, a week before commitment, had a spell of unconsciousness for several hours. Afterwards speech was thick and restlessness, insomnia, and a vagrant tendency set in.

Before commitment had visual hallucinations. Fabulation. Tremors. Conjunctivæ injected; eyes "excited looking." Patient swept things from dining room table. Drew a hot stove into the middle of the room. Attempted to sweep paint off the floor and cut up the carpet with a knife. The patient on commitment November 5, 1904, was well developed and nourished. The mucous membranes were rather pale. Bruises and excoriations of limbs. Harsh breathing at the base of each lung. Enlargement of heart; sounds irregular. Accentuation of aortic second sound; tension fair, rate 80. Slight brachial arteriosclerosis. Abdomen slightly distended. The urine contained a faint trace of albumin and many hyaline casts.

Moderate tremor of extended hands. Slight tongue tremor. Romberg's sign absent (slight swaying). Considerable ataxia of extremities (inability to stand with foot on opposite knee). Vision poor. Hearing could not be tested accurately. Prompt pupil reaction with direct light. Slight consensual reaction in left pupil, absent in right. Deep reflexes equal and lively.

Quiet and orderly at first. Later restless and noisy. Questions were answered somewhat relevantly, more often irrelevantly. Patient irritable, intractable. Required repeated urging to take nourishment. Consciousness clouded. Orientation imperfect. Attendants are possibly "officers." Date September, 1995. Slight errors in repeating alphabet. Mistakes in Lord's prayer with rhyming tendency. Simpler arithmetical tests answered automatically with many mistakes. More complex combinations incorrect. Hand writing tremulous (noted as "typical" of general paresis). Auditory hallucinations (answering invisible persons), "All right, I am coming." Amnesia and fabulation. Q. "Have you had breakfast?" A. "No," (later), "Yes, I had a very light breakfast." Q. "What did you have?" A. "Anything that came along. A few green peas and beans that were left, bread and butter and pie. I had a good breakfast. Guess feed is very high." Q. "Give names of your sisters and brothers." A. "There are three or four I never see. I will have to think them up." (Later)—"Lillie, Abbie, Julia, George." On repetition of question, "Elizabeth, Julia, Annie and Lizzie."

Delusions somewhat doubtful. At no time euphoria.

The patient remained only nine days in the hospital, developing diarrhea a week after admission.

Post Mortem Findings.—The *cause of death* was bilateral bronchopneumonia of hypostatic distribution, accompanied by bronchitis and acute splenitis. The intestinal tract was normal (despite the clinical diarrhea). No cultures. The heart showed acute myocarditis.

The vessels in general showed no sclerosis, except that the aorta showed a few patches with calcification near bifurcation. There was a moderate degree of mitral sclerosis. The kidneys showed a moderate degree of chronic interstitial nephritis. The heart weighed 530 grams and there was moderate dilatation of all the valves.

There were some evidences of *chronic disease outside the nervous system,* namely, an obliterative pleuritis on the right side, chronic perisplenitis, and chronic external adhesive pachymeningitis.

The *nervous system* showed a pia mater thin and transparent, with a moderate congestion of larger and smaller vessels. No noteworthy change of the brain substance or of the ventricles was found, except that the cerebral substance was of unusual firmness (autopsy twelve hours after death).

The fourth case of diagnostic error was that of J. B., D. I. H., 12486, Path. Lab. 1011.

J. B., male, printer. Born 1855 in England. Relatives are said to have been generally long lived.

Personal History.—Married in 1875 (two children, healthy; again married in 1893 (one child, healthy). Compositor from 1890. In 1898 and 1899 girdling and lancinating pains. Thereafter for several years gait was unsteady. During 1904 and 1905 freedom from pains and improvement in gait but gradually increasing irritability and nervousness. Stopped work on the last of March, 1905, owing to sudden increase of irritability, emotionality, boastfulness, expansive schemes, and ataxia.

Habits: no tobacco, very little alcohol at long intervals. No drug habits, no sexual irregularity known.

Committed to D. I. H. April 3, 1905, with slight muscular development, poor nutrition, acne, irregular poorly preserved teeth, gingivitis, flat-foot, slight radial arteriosclerosis, slight arcus senilis, a few hyaline cases, leucocytes, epithelial cells, and trace of albumin in the urine, scar in sulcus, and enlarged inguinal lymph nodes.

Ataxic gait, Romberg's signs, fibrillary twitching of chest, abdominal and facial muscles when standing; right pupil slightly larger than left, pupillary margins irregular, light reactions (electric bulb test) both consensual and direct absent, slight pupillary reaction in accommodation; biceps, triceps and wrist reflexes lively and equal; abdominal, cremasteric and plantar reflexes normal, knee jerks, Achilles and front taps negative even on reenforcement.

The patient himself stated that his ataxia began in 1904, that he had been under treatment for swelling of legs and feet and pain in limbs since 1903, and that there had been some trouble with limbs since 1895. He had been told that his disease was lead-poisoning. About three weeks before commitment patient said he had had an attack of unconsciousness.

The patient's speech showed considerable defect. Words were pronounced slowly with slurring and tripping especially of the labials. Orientation perfect. School knowledge well retained. The easier arithmetical problems were accurately performed. Memory imperfect for minor recent events. Estimations of space and time often very imperfect. Variability of mood, sometimes euphoric sometimes tearful and irritable. Occasional expansive estimates of personal powers ("Can lift three five-hundred pound weights with one finger"). Indistinct expansive financial ideas.

The patient continued oriented, euphoric, expansive, untidy till October, 1905, but on October 12 developed an infection at the site of a callus on the sole of the foot and died with pyemic symptoms, October 17.

Post Mortem Findings.—The *cause of death* was streptococcus septicemia with acute ulcerative colitis, acute splenitis, bilateral purulent pleuritis, multiple infarctions of lungs.

There were no signs of *chronic disease outside the nervous system* except a moderate thickening of the mitral valves, and slight dural adhesions.

The brain weighed 1,450 grams. The vessels at the base showed a slight degree of sclerosis. There was a slight opacity of the frontal, parietal, and temporal lobes overlying slightly atrophied convolutions, whose surfaces showed in a few places slight cuppings. The ependyma over the thalami and the floor of the fourth ventricle was finely roughened. The spinal cord showed a typical tabes dorsalis.

The fifth case of diagnostic error was that of C. E., D. I. H. 13829, Path. Lab. 1251.

C. E., female. Born 1859. Normal school girl till 15, apt in studies, mill worker till marriage at 18, one child, dead (cause unknown). Habits good. Moderate deafness set in in the patient's forties and in 1901 patient became suddenly completely deaf in three months time. In 1905 she became unable to take care of her house and had a shock in which the right leg was affected.

On commitment patient showed good development and nutrition with slight enlargement of capillaries of cheeks, redness and roughening of skin of right ankle. Teeth absent. Slight radial and brachial arteriosclerosis. Urine negative.

Sluggish pupil reactions to light both directly and consensually. Deafness absolute, bone conduction defective. Arm reflexes brisk, knee jerks equal, brisk. Bilateral Babinski reaction more marked on the right side, tremor of tongue, Romberg's sign, gait defective. Speech stumbling, writing clear, without tremor.

Communicated by writing only. Consciousness normal, disorientation for day of month, for place (misnames hospital) and for persons (recognizing nurses, not patients).

Patient wrote many letters complaining of pain, headaches and especially of pain in the abdomen and side. The patient was thought to show a slight defect of memory, but her deafness rendered diagnosis difficult. The patient died suddenly on May 23, 1908, shortly after supper, falling backwards, and dying in five minutes with marked respiratory distress.

Post Mortem Findings.—The *cause of death* was not clear. The heart's blood and cerebrospinal fluid were sterile. There was a small hemorrhage in the anterior part of the right ventricle derived from a small artery of the caudate nucleus. There were about 400 c.c. of blood between the dura mater and the pia mater. There was a slight sclerosis of the basal and Sylvian arteries. The brain substance was uniformly softer than normal.

It is possible that the hemorrhage had taken place sometime before the patient's fall and that the brain substance had swollen in consequence. Just before the patient's fall she had had a weeping spell.

The anatomical diagnoses were as follows:

Anatomical Diagnoses.—Obesity, unequal pupils, fresh wound near left ear, edema of legs, slight focal adhesive pleuritis, hypostatic congestion of lungs, chronic endocarditis, chronic myocarditis, congestion of kidneys, congestion of pancreas, subacute splenitis, chronic adhesive pelvic peritonitis, hematoma and cystic condition of Fallopian tubes, calvarium dense and thick, subdural hemorrhage, slight chronic leptomeningitis, general cerebral atrophy, marked in tips of frontal lobes, old cyst of softening between left corpora albicantia and optic chiasm, small punctures of left ear drum, drums opaque, chronic spinal leptomeningitis, brain weight, 1,190 grams.

The spinal cord showed firm adhesions between dura and pia throughout. A lumbar puncture soon after admission in 1907 had shown:

	Per Cent.
Endothelial cells	10
Lymphocytes	30
Plasma cells	0
Phagocytes	0
Polymorphonuclear cells	51
Unclassified	9
Fibroblasts	0
Cells in 100 fields	125

The sixth case of diagnostic error was that of H. W., colored, D. I. H., 13832, Path. Lab., 1257.

H. W., male, born 1871. Learned to read and write at school. Stableman and coachman. Alcoholic till 1902. Took much quinine, possibly impairing hearing thereby. Memory impaired and growing worse since 1902. Gait unsteady for a longer but unknown period. August 13, 1907, wandered about, instead of attending boot-black stand, muttered, talked incoherently. In the next few days talked about religion and apparently had hallucinations of hearing. Committed August 16, 1907. On commitment stoop-shouldered, flat-chested. Gait straddling. Unsteadiness in Romberg's position. Incoördination of arms and fingers. Coarse tremor of tongue. Tremor of lower jaw. Exaggeration of left knee jerks and diminution of right. Exaggerated Achilles jerks. Spurious left ankle clonus. Questionable Babinski reaction of left side. Abdominal and epigastric reflexes present but cremasteric absent. Left pupil smaller than right and fails to react to light. Reaction of right pupil sluggish. Moderate defect of hearing of both sides.

During the first week the patient developed hallucinations of sight and hearing, but of no other senses. Disorientation for time, place, and persons. Answers to arithmetical problems given with assurance but as a rule incorrectly (as 17 and 32 are 90; 18 divided by 3 = 88). Handwriting scarcely legible Memory poor, especially for recent events (recalled a lumbar puncture as an exercise in baptism). Impressibility and attention poor. Euphoria. Death after gradual failure July 29, 1908.

Lumbar puncture showed:

	Per Cent.
Endothelial cells	9
Lymphocytes	81
Plasma cells	6
Phagocytes	0
Polymorphonuclear cells	4
Unclassified	0
Fibroblasts	0
Cells in 100 fields	700

Post Mortem Findings.—The cerebrospinal fluid showed a pure culture of *Bacillus coli communis,* and the heart's blood showed many colonies of an unidentified bacillus. Culture from mesenteric lymph nodes sterile.

The *cause of death* is somewhat in doubt. There was an early pneumonic process with fibrinous pleurisy, and there was an early acute hemorrhagic ileitis with a very slight overlying peritonitis and slight corresponding enlargement of mesenteric lymph nodes. There was an infection of the meninges with *Bacillus coli communis.*

Evidences of *chronic disease outside the nervous system* were: coronary and pulmonary arteriosclerosis, chronic fibrous endocarditis, mitral sclerosis, aortic sclerosis with calcification, chronic splenitis, chronic interstitial nephritis, hepatic atrophy (?, 900 grams), thickening of cartilaginous portion of right auricle (old trauma?), scars of apices of lungs.

The *calvarium* was dense and the *dura mater* everywhere adherent. The *arachnoidal villi* were but slightly developed, but there was one small focus of cortical herniation through the dura mater of the left middle cranial fossa. The *pia mater* was delicate except for slight opacities along sulci. There was some pial thickening over the region of the interparietal sulci on both sides. There was pial pigmentation anteriorly and superiorly. There is no gross evidence of intracranial arteriosclerosis, except (1) that afforded by the lesions of the dentate nuclei of the cerebellum mentioned below and (2) the swerving to the right of the basilar artery, possibly due not to arteriosclerotic lengthening of the artery but to an unusual shape of the pons (see below).

The *brain* weighed 1,245 grams (cerebellum and pons 165 grams). The anatomical diagnoses of central nervous system were:

Slight general encephalomalacia (post mortem imbibition of fluid, 31 hours). Slight gliosis of right prefrontal and frontal gyri. Slight gliosis of right optic thalamus. Generalized granular ependymitis, especially near fornix and about foramina of Monro. Anomaly of pons (not gliotic, but possessing far more white matter on the left side than the right). Severe arteriosclerosis confined to the dentate nuclei of the cerebellum.

Microscopic Examination.—The microscopic examination was carried out *for the purpose of learning whether,* in addition to the various evidences of nerve cell destruction and gliosis which might be consistent with the diagnosis of general paresis, *the tissues showed plasma cells.* Although it is well established that plasma cells occur in brain tissues in other conditions than general paresis (e. g., trypanosomiasis and certain other chronic meningoencephalitides) and although the cytology of the lumbar puncture fluid may be identical in general paresis and in tuberculous meningitis, yet it seems certain that the diagnosis of general paresis cannot be regarded as fully established unless plasma cells are demonstrable either in the lumbar puncture fluid or in the brain tissues. So much must now be assumed as a result of the labors of the Nissl school.

For the identification of plasma cells, Nissl's original methylene blue method (with certain inessential modifications) and the pyronin method of Leo Ehrlich (a production of the Unna school) were used in all cases.

The superior frontal, precentral, superior temporal and calcarine gyri of the cerebrum, several cerebellar areas, and three levels of the spinal cord, fixed in alcohol, were examined as routine in all the cases. In the special cases of erroneous diganosis just described, a varying number of additional blocks was also subject to examination. Although it must be conceded that, strictly speaking, the whole brain must be gone over if one is to exclude absolutely the presence of plasma cells in some focus, yet I believe we can be reasonably certain of the correctness of these particular diagnoses. This belief is justified both by the anatomical features of the cases and by the possibility of explaining the clinical features of the cases on the ground of other positive (non-paretic) changes.

Grouping of Cases.

Thus anatomically we may sum up the cases as follows:

I. Tabes dorsalis and severe progressive arteriosclerotic brain atrophy.

II. Cysts of softening in both dentate nuclei of cerebellum and diffuse brain atrophy.

III. Cerebral sclerosis.

IV. Tabes dorsalis and slight atrophy of frontal, parietal, and temporal gyri.

V. Chronic spinal meningomyelitis, diffuse brain atrophy (especially prefrontal), and focal encephalomalacia.

VI. Severe arteriosclerosis confined to dentate nuclei of cerebellum and slight sclerosis of right prefrontal and other frontal gyri and of right optic thalamus.

From this analysis it is clear that the cases fall into three groups: I and IV showed a combination of more or less severe brain disease with *tabes*. II and VI showed a combination of more or less severe brain diseases with a striking *cerebellar involvement* (evidences of arteriosclerosis in the dentate nuclei). V was a case of marked meningomyelitis and subcortical encephalitis (luetic?). III was a case in which slight cerebral sclerosis was the only anatomical finding.

A. Confusion of General Paresis With Meningomyelitis and Subcortical Encephalitis.

Case V gives evidence of marked cortical destruction. Perhaps no layer of the cortex in all the areas examined fails to show some atrophic alteration. But the suprastellate layers are everywhere more severely diseased. In particular the layer of moderate-sized pyramids seems to show a fairly even atrophy throughout, whereas the layer of small pyramids and the layer of large external pyramids are more focally affected. Satellitosis accompanies the atrophic process in many regions. Subpial gliosis is a constant feature. The white matter in all areas shows a considerable increase of neuroglia.

Unlike the other two cases of the tabes group (I and IV), this case shows *lymphocytic deposits.* These are decidedly subordinate in the cerebral cortex, cerebellum, and basal ganglia to the evidences of nerve cell destruction; but perivascular infiltrations, confined to a few of the larger vessels of the white matter, are found in superior frontal, superior temporal, and hippocampal gyri.

But in the *spinal cord* the most severe infiltration is in the gray matter, where it accompanies severe nerve cell changes and extensive arterial changes. The spinal meninges are also packed with mononuclear elements (among which, however, no plasma cells are found). Appropriate stains demonstrate an extensive loss of medullated fibers in a broad peripheral zone running all the way about the cord at most levels, but almost constantly about the anterolateral columns. Vascular changes and mononuclear infiltrations accompany this marginal sclerosis, penetrating the cord to an unusual distance.

The distribution of these lesions recalls a case described by Putnam and the writer in which there was good evidence of syphilis. In this case the evidence is not so good; but the case is clear so far as the main diagnostic features are concerned.

An instance of active meningomyelitis and subcortical encephalitis with atrophic changes in the cerebral cortex has therefore been confused diagnostically with general paresis. An indication of the possible line of differentiation in future cases is afforded by the cytology of the lumbar puncture fluid, which yielded lymphocytes but *no plasma cells.* Without this laboratory aid, the diagnosis must remain difficult. It is probable that the Wassermann reaction would prove of no differential aid in this particular difficulty.

B. Confusion of General Paresis With Tabes Dorsalis Plus Non-Paretic Cerebral Disease.

Combinations of mental symptoms of whatever sort with the phenomena of tabes dorsalis will doubtless raise in most medical minds the suspicion of general paresis. This has become the more true now that a significant part appears to be played in both tabes and general paresis by antecedent syphilis. Some are inclined to hold to the identity of the two diseases. The general resemblance of lumbar puncture fluids (cytology) in the two diseases also lends color to the identification.

The lesions of the two diseases are, however, quite distinct, and their genesis, were it understood, would undoubtedly show important differences.

Nothing could be clearer than the combination of lumbosacral tabes with multiple foci of encephalomalacia presented by case I. Outside the foci of encephalomalacia the cortex is in a good state of preservation, except that subpial gliosis is almost everywhere marked.

Case IV microscopically presents in all areas examined a high degree of satellitosis. The satellite cells accumulate so as often to appear in groups of eight or ten about atrophying cells. Such satellite cells often occupy niches in atrophying nerve cells. The process is most abundantly shown in the layer of large external pyramids (e. g., motor), but is also shown in the infragranular layers. The infragranular layers as a rule, in this case, are comparatively poor in cells.

The satellitosis and nerve cell destruction were found in approximately equal degree in all blocks examined from case IV. Perivascular cell accumulations were slight, and consisted of pigmented cells and a few mononuclear cells somewhat suggestive of lymphocytes. But no undeniable lymphocytes and no plasma cells were found.

The tabes was striking, but there was no evidence of pyramidal tract disease in Weigert preparations of the spinal cord.

C. CONFUSION OF GENERAL PARESIS WITH ARTERIOSCLEROTIC BRAIN DISEASE HAVING SEVERE CEREBELLAR INVOLVEMENT (DENTATE NUCLEI).

Of the two cases in this group, II showed somewhat questionable Argyll-Robertson pupils and VI showed an Argyll-Robertson effect in one pupil only. Both showed Romberg's sign as well as certain alterations in deep reflexes.

The unqualified assertion that cerebellar disease had been the chief cause of diagnostic error in these cases would be unwarranted.

The spinal cord was not quite normal in either case. Case II showed a tabetiform lesion in the cervical cord (not elsewhere), together with a unilateral degeneration suggesting in some respects a radicular origin (high thoracic or low cervical). Case VI showed no tabetiform lesions, but in all segments examined an unusual display of corpora amylacea of wide distribution, as well as a moderate lymphocytic infiltration of the meninges. On the whole, however, it does not seem possible to relate the tabetic symptoms with certainty to any spinal cord lesion in Case VI.

What part can be assigned to dentate nucleus involvement? Case II, in which the dentate nuclei were in large part destroyed by cysts of softening, shows a fairly well-preserved cerebellar cortex on both sides (moderate gliosis of Purkinje cell belt with some loss of Purkinje cells).

Case VI, in which the dentate nuclei were not destroyed but affected by cell atrophies of variable degree in various parts of the dentate convolutes, showed severe gliosis of the cerebellar cortex, involving more particularly the Purkinje cell belt and the molecular layer, but also to some extent the granule layer. In the regions so far examined the left hemisphere of the cerebellum is more severely diseased than the right.

Comparing the cerebral cortex in the two cases, we find some differences. Case II shows little more than a fairly even degree of subpial gliosis in all regions, together with a varying degree of atrophy rather generalized in the different layers and marked neuroglia cell pigmentation. Case VI showed far more marked generalized cell atrophies throughout the layers with considerable subpial gliosis. Perhaps the superior temporal gyri showed the most marked cell atrophy.

The comparative analysis of these two cases seems to exclude cortical disease from playing much part on the neurological side, and even on the psychiatric side the data are equivocal. Since only one of the cases showed a well-defined spinal cord disease (and this of limited character and but doubtfully related with the neurological symptoms), it seems possible, at least, that the cerebellar disease in the two cases played some part. It seems especially possible that the Romberg phenomena may be related therewith. But it is obvious that further experience with dentate nucleus disease is necessary for a decision.

D. Confusion of General Paresis With Cerebral Sclerosis (Type, Perivascular Gliosis).

This case has been previously reported by Mitchell and the writer in their analysis of insanity arising in the sixth and seventh decades (Case 9), but without mention of the striking fact that the examiner (Dr. F. R. Sims), as well as Drs. A. M. Barrett and H. W. Mitchell, were all disposed to make the diagnosis "general paresis." An examination of all the data in the case leads to the conclusion that the case belonged rather in the "probable" than in the "certain" group (see table, *supra*).

Microscopically, case III showed some features of interest, especially multiple focal neuroglia-cell proliferations of a perivascular distribution, considerable subpial fibrillar gliosis of an unusually focal type, and a rather general subpial cellular gliosis. The findings seem to argue a progressive or at all events an active process, and a process starting not so much in relation with dying nerve cells as in the neighborhood of the vessels.

The acute or cellular perivascular glioses are very striking lesions. They are confined almost exclusively to the substellate (infragranular) cortical layers, sometimes trenching slightly on the layer of stellate cells and occasionally wholly included in the white matter in the immediate vicinity of the gray.

In the absence of bacteriological examination, it is rash to suggest the possible nature of this case. Perhaps the cortex findings indicate the effect of a toxine, as many of the autopsy data indicate possible septicemia.

At all events the brain was not wholly normal, exhibiting slight general induration due in part to subpial gliosis and in part, doubtless, to perivascular gliosis. The more serious involvement of the infragranular cell layers suggests obvious comments concerning function; but these must be postponed until other cases of this kind have been studied.

The diagnosis of general paresis in this case was, therefore, not justified. Although at first sight it may seem odd that cerebral sclerosis should clinically imitate the meningoencephalitis of paresis, yet the perivascular distribution of the most recent gliotic processes in the cortex suggests the possibility that non-exudative lesions may sometimes imitate exudative lesions *in clinical effects.*

CONCLUSIONS.

1. An effort has been made to establish the accuracy of diagnosis in general paresis. The method has been to analyze clinically the data of cases in which several experienced workers had agreed upon the diagnosis and to compare their findings with the anatomical and histological data of the autopsies.

2. 35 out of 41 cases unanimously diagnosed general paresis ante mortem proved to be cases of general paresis (85 per cent. accuracy).

3. 6 cases of erroneous diagnosis have been especially studied. None of these showed plasma cells in the nerve tissues (Nissl's

methylene blue and L. Ehrlich's pyronin methods), but all showed a variety of lesions which warrant placing them in an "organic" group.

4. The lesions probably responsible for the errors in diagnosis were: (*a*) Meningomyelitis and subcortical encephalitis (luetic?), case V; (*b*) tabes dorsalis and non-paretic cerebral disease, cases I, IV; (*c*) arteriosclerotic brain disease with severe cerebellar involvement (dentate nuclei), cases II, VI; (*d*) cerebral sclerosis (type, perivascular gliosis), case III.

5. Although at first sight a probable error of 15 per cent. in the diagnosis of general paresis might suggest difficulties in possible medicolegal cases, it is obvious that, were the diagnosis confined to "incurable insanity" or even to "organic brain disease," the error would disappear. However, 2 cases proved to be general paresis (on the plasma-cell criterion) in a series of 186 cases similarly examined in which the diagnosis of general paresis was not considered.

6. Improvements in our diagnostic ability could perhaps be introduced by lumbar puncture and cytological examination in a greater proportion of cases. But, it is doubtful whether three of the six errors here studied would have been resolved by cytodiagnosis (meningomyelitis, tabes dorsalis). One other case (VI, arteriosclerotic brain disease) actually did show plasma cells in the lumbar puncture fluid, the source of which was not made out at autopsy.

XXIII

ANATOMICAL FINDINGS IN SENILE DEMENTIA: A DIAGNOSTIC STUDY BEARING ESPECIALLY ON THE GROUP OF CEREBRAL ATROPHIES.*

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CONTENTS.

PAGE.

The daily clinics of the Danvers State Hospital........................ 674

Accuracy of diagnosis in
  General paresis 674
  Senile dementia 675

Proportion of senile dements with and without 1) cerebral atrophy and 2) cortical arteriosclerosis................................ 676

Standard of cerebral atrophy adopted.................................. 676

Cortical arteriosclerosis 677

Proportion of macroscopically "normal" cases........................ 678

Incidence of focal lesions, Nötzli, Meyer, Appeldorn, the writer....... 678

Clinical and anatomical summaries in eight relatively pure atrophic cases 679

General clinical analysis of the eight atrophic cases as to
  Sex 685
  Heredity and antecedent factors.................................. 685
  Social factors 687
  Defects of vision and hearing..................................... 687
  Relation to manic-depressive insanity.............................. 688
  General and visceral arteriosclerosis.............................. 689
  General clinical features... 689
    Neurological 690
    Psychiatric 691
  Age, onset, and duration (table).................................. 693

General anatomical analysis as to
  Gross anatomy of the brain.. 693
    Nötzli's hypothesis 695
    Meyer's data 697

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* Read in part at the Annual Session of the American Medico-Psychological Association, Atlantic City, N. J., June, 1909.

Appeldorn's data 698
Ratios of actual to calculated weights of brain and of heart, liver, kidneys (combined) 698
Comments of Alzheimer 699

Chronic non-nervous conditions

Arteriosclerosis 700
Heart disease 700
Kidney disease 701
Other chronic conditions 701
The cause of death 701
Discussion and microscopic analysis 701
"Neuronophagia" and Metchnikoff's hypothesis 703
Positions assumed by satellite cells 703
Relation of vascular to atrophic changes 704
Conclusions 704
References 707

I have lately possessed the unusual advantage of reviewing a considerable collection of autopsies (247) upon cases of mental disease introduced at various times in the years 1904-1908 at the daily clinics of the Danvers State Hospital, Massachusetts. The cases introduced in these clinics are of particular value, because the often divergent opinions of several diagnosticians, from three to eight or more, are recorded in each instance. The staff has varied from time to time, but has at all times contained members familiar in our recent American psychiatric literature, such as Prof. A. M. Barrett (now of Ann Arbor), Dr. H. A. Cotton (now of Trenton, New Jersey), Dr. H. W. Mitchell (now of the Eastern Maine Hospital for the Insane), Dr. H. M. Swift, and Dr. Charles Ricksher, as well as the moderator, Superintendent Charles W. Page. The clinical diagnoses which I have considered have not been those chosen for the statistical records required for the Board of Insanity, but *all* the diagnoses rendered for each case.

For more minute examination I have naturally resorted to those cases in which all the staff agreed, holding the opinion that uniformity in diagnosis by several men is of more value than that induced by a single chief of clinic.

To establish the degree of accuracy in diagnosis at these clinics, I may mention (what I have dealt with more specifically before the American Neurological Association) the 85 per cent accurate diagnoses where all agreed to general paresis. Only 6 out of 41 cases *unanimously* diagnosed general paresis turned out to be cases of something else. The reasons for these 6 incorrect diagnoses I shall present *in extenso* elsewhere,[1] but they do not militate against the general accuracy of diagnosis in the Danvers daily clinics.

I was the more astonished to find that, on accepted anatomical criteria, our success in the diagnosis of senile dementia at these clinics was not at all comparable with our surprisingly good results in general paresis. On the hypothesis that cerebral atrophy is a necessary feature in senile dementia, our diagnoses turned out to be only 38 per cent correct. On the hypothesis that cortical arteriosclerosis is a necessary feature in senile dementia, our diagnoses were but 48 per cent correct. And, in fact, 14 of the 42 cases in which the diagnosis of uncomplicated senile dementia was rendered, viz., 33 per cent, proved to show neither sclerosis of terminal arteries nor cerebral atrophy, so that *our general percentage of accuracy, as established by the finding of either cerebral atrophy or cortical arteriosclerosis (or both), was 66 per cent for senile dementia.*

The general analysis of this material may be presented in the following table, which deals with the data of 42 uncomplicated cases in a total of 71 cases of probable senile dementia in a grand total of 247 cases of various types of mental disease subject to anatomical review:

Diagnosis of Senile Dementia.

Clinically uncomplicated		42
Brains underweight		29
Males under 1358 G.	10	
Females under 1235 G.	19	
Brain atrophic		11
At least one-sixth loss in weight.		
Brains atrophic		16
All data considered.		
Sclerosis of cerebral end-arteries		20
Atrophic, not arteriosclerotic		8
Not atrophic, not arteriosclerotic		14

These 42 cases have been subjected to closer analysis with the object of determining the necessary features in a case of senile dementia.

It does not appear that the anatomical and histological characters of senile dementia are as clear-cut and ready of diagnosis as the post-mortem characters of general paresis. But there is a widely current opinion that the brains of senile dements show well-marked *cerebral atrophy*. Other descriptions give equal prominence to *arteriosclerotic lesions*. Frequently the literary student gains the impression that both kinds of disease characterize the brains of senile dements, or even obtains a thinly-veiled conception that the brain atrophy is somehow due to arteriosclerosis.

Cerebral Atrophy.

With respect to cerebral atrophy, it appears that there is actually no standard by which to determine the amount of loss in weight which shall signify atrophy. Thirteen of the brains in the 42 uncomplicated cases of senile dementia, remarkably enough, yielded weights above the averages ordinarily assigned for male (1358 grams) and female (1235) grams. Thus, unless some of these 13 cases possessed unusually large brains at the outset (of which there is no evidence otherwise), we need consider only 29 cases as belonging possibly in the cerebral atrophy group.

There is, however, no warrant for the diagnosis of cerebral atrophy in every case which is somewhat underweight with respect to the assigned averages of the books, since we must take into account initial differences in brain weight (variations according to race, body weight, stature, age). Thus brain weights ranging from 1461 to 1265 have been assigned to average normal males, and weights from 1341 to 1112 to average normal females.[2]

It is obvious, therefore, that the degree of loss which is to warrant the diagnosis "atrophy" is hard to determine. Perhaps, in the last resort, we should be dissatisfied with any result which did not depend on an obviously impossible calculation—namely, the degree of loss from the original weight in the given case.

If in this series we adopt the arbitrary standard sometimes advocated—namely, a conceived loss of one-sixth the original weight[3]—and take the ordinarily assigned averages as original weights, we at once reduce the cases showing brain atrophy to 11. Thus only 26 per cent of 42 cases diagnosed as senile dementia would show atrophic brains.

Perhaps it is better to trust the qualitative data with respect to the diagnosis, cerebral atrophy. Upon collation of the qualitative findings, paying attention to the occurrence of both diffuse and focal atrophies of convolutions, the same result as before recorded (on the criterion of weights) was registered for the incidence of brain atrophy. There were 13 cases which could not be regarded as atrophic and 29 which showed either diffuse or focal convolutional atrophy. The distribution of these classes was almost the same as the distribution of the weight classes. Two cases were carried over from the larger class (29) to the smaller (13). (The first on the score of focal atrophy of one frontal region, the second on the score of a focal lesion (possibly aplasia) of the frontal lobes). And two cases were carried in the reverse direction from the smaller class (13) to the larger (29) on the basis of exact gross descriptions, suggesting approximate normality of convolutions.

But the atrophies which were employed to separate these two classes were not all diffuse atrophies such as we have in mind in the current definitions of senile dementia. Only 20 of these cases showed an obvious diffuse cerebral atrophy, and of these four showed a slight or a questionable atrophy. Thus, if the gross qualitative differentiæ are adopted, 16 out of 42 cases of senile dementia (or 38 per cent) showed cerebral atrophy of a convincing character.

Cortical Arteriosclerosis.

A review of the gross and microscopic findings indicates that we cannot safely exclude cerebral arteriosclerosis of greater or less degree in any single case of this series of 42 cases. (Four cases in which no specific note was made of cerebral arteriosclerosis yield other data, gross or microscopic, from which some degree of such change can be assumed.) Similar statements probably hold good of many brains in the non-insane in advanced age.

But it is evident that there are important theoretical differences between cases which show sclerosis of the larger anastomosing arteries and those which show sclerosis of terminal arteries. Sclerosis of the terminal arteries of the brain, whether leading to infarctions or not, obviously means much more from the standpoint of the integrity of the cerebral functions. In fact it would seem difficult to exclude with certainty cases of extensive small-branch arteriosclerosis from the group of organic dementia.

Twenty out of 42 cases diagnosed senile dementia proved to show a significant arterial disease—sclerosis of terminal cerebral arteries, leading to gross or microscopic infarctions in 16 instances. Although the other 22 of the series showed arteriosclerosis also, this sclerosis was confined to the circle of Willis or to the proximal portions of the primary branches of the circle, so that the changes were deemed of no special psychiatric importance, beyond that which may attach to sclerosis of the pipe arteries throughout the body. Although it may be scarcely justifiable to transfer these 20 cases of small-branch arteriosclerosis bodily over to the group of organic dementia, since many of the symptoms shown may have been due to quite other causes than the arteriosclerosis shown, still it is manifestly unwise to study such cases from the standpoint of a critical symptomatology under the impression that they are pure instances of senile (not organic) dementia.

Cases Without Sclerosis of Cerebral End-Arteries.

An analysis of this residuum of 22 cases not showing significant cortical arteriosclerosis (either focal encephalomalacia or other evidence of sclerosis of terminal cerebral arteries) shows that eight belong frankly in the atrophic series, whereas 14 stand out as cases in which neither diffuse cerebral atrophy nor sclerosis of terminal cerebral arteries can be ascribed to the brains.

Should this prove an adequate analysis of the anatomy of these cases, it is plain that, in the histories of the eight simple atrophic cases, we might find data corresponding to our conception of senile dementia (providing cerebral atrophy is a necessary feature of this disease). And in the histories of the outstanding 14 we might expect a variety of data in which the characteristic features of senile dementia are lacking.

That somewhat similar results might be expected in a large series of cases, at least in so far as the exclusion of arteriosclerotic cases as " organic " is concerned, is seen from the following table compiled from writers, mentioned again below:

Focal Lesions in " Senile Dementia."

Nötzli, 1895	19	13	32
Meyer, 1896	11	13	24
Appeldorn, 1908	18	14	32
Southard, 1910	20	22	42
	68	62	130

Cases of Cerebral Atrophy.

The following pages are devoted to brief clinical summaries of the eight supposedly pure brain atrophy cases, together with the main anatomical diagnoses in each case.

The special features of the different brains are discussed together on a later page.

Case I.—D. I. H., 11801, Path. Lab. 872. Woman, born 1823. *Heredity:* Father and two brothers died of senile dementia. Mother died of asthma. *Personal history*: Normal in girlhood. Taught school. Married 1843; 9 children (four living in 1904); one miscarriage. Of a melancholy turn. Delirious during a fever, 1874. Fractured thigh, 1897, after which came mental change; amnesia, fabrications, apathy. Cut up clothes. Numerous dreams. Fearful, often said she was dying.

Committed to D. I. H., 1904. Emaciation, anemia, senile skin, teeth absent, feet blue, muscles flabby and weak, arcus senilis. Double cataract, blind, pupils non-reactive, somewhat deaf, tongue and face muscles finely tremulous, too weak to walk or stand, slight paraphasia (?), cannot write, radials and brachials thick and tortuous, pulse thready, irregular, and faint (90 to 100), organic reflexes altered.

Disorientation for time, place, and persons. Amnesia for recent and remote events. Impressibility poor. Multiplies as far as 3 x 5, and adds 2 and 2, but does no further tests. Resistive, restless.

Death 15 days after admission.

The autopsy showed *chronic conditions:*

Malnutrition.

Marked general arteriosclerosis, with calcification and ulceration of aorta, extensive coronary sclerosis, and moderate involvement of bases cerebral arteries.

Bilateral generalized pleural adhesions.

Scar of right apex.

Chronic diffuse nephritis.

Brown atrophy of heart muscle.

Slight chronic passive congestion of liver.

Slight chronic localized peritonitis (omental).

Diffuse cerebral atrophy.

And much evidence of *acute disease:*

Acute sphenoidal, ethmoidal, and occipital sinusitis.

Bilateral bronchopneumonia, with acute bronchitis and tracheitis (without lymphnoditis).

Edema of left side of rima glottidis.

Lung cultures yielded staphylococci, streptococci, pneumococci, and a bacillus of the pseudodiphtheria group.

Culture from the ethmoidal sinus yielded S. p. aureus, but culture from sphenoidal sinus remained sterile.

The *cause of death* was undoubtedly bronchopneumonia.

Case II.—D. I. H., 11716, Path. Lab. 849. Woman, born 1818. *Heredity* and much of *personal history* unknown. Onset said to be in 1900 after a fall. (Gall-stones and chronic fibrous peritonitis at autopsy.) Widow.

Committed to D. I. H., 1904. Malnutrition, senile skin, arcus senilis, teeth absent, musculature poor, right eye blind, right pupil fails to react to direct light, hearing somewhat defective, left knee-jerk, elbow and forearm reflexes exaggerated, tremor of tongue, labial tremor when talking, right leg weaker than left and kept flexed, incoordination in movements of feet, muscular sense in legs diminished, radials and brachials thickened and tortuous, pulse full, regular, 96.

Excited and resistive on admission. Disorientation for time, place, and persons. General amnesia. Fabricates (assigning wrong names).

The autopsy showed *chronic conditions:*

Obesity.
Aortic sclerosis with ulceration.
Mitral sclerosis.
(Coronary arteries normal.)
Diffuse and focal sclerosis of basal cerebral vessels.
Chronic fibrous endocarditis.
Chronic adhesive pleuritis, left.
Calcified and caseous nodule in central part of left lower lobe.
Scar of right apex.
Chronic nodular perisplenitis.
Cholelithiasis.
Moderate chronic passive congestion of liver.
Fatty liver.
Chronic diffuse nephritis.
Chronic localized peritonitis.
Chronic external adhesive pachymeningitis.
Diffuse cerebral atrophy.

Acute conditions:

Edema of left leg (thrombosis?, not proved).
No cultures were taken from this case and the cause of death is doubtful.

Case III.—D. I. H., 11881, Path. Lab., 1050. Woman, born 1834. Almshouse transfer to D. I. H., 1904. Nutrition and musculature fair. Senile facies and skin. Arcus senilis. Varicose veins. Teeth almost all absent. Radial arteries not palpably sclerotic. Vision and hearing impaired.

Pleasant, garrulous, Irishwoman, speaking mixture of English and Gælic. Knew month and day of week, but not the year. Repeated Lord's Prayer. Counted from 1-20, performed a few of the simplest problems. Amnesia for remote events, not so marked for recent events. Cannot write or read.

Death in 1906.

The autopsy showed *chronic conditions:*

Cardiac hypertrophy.
Coronary, splenic, and renal arteriosclerosis.

Brown atrophy of heart.
Chronic passive congestion of lungs.
Slight portal cirrhosis of liver.
Chronic diffuse nephritis.
Chronic perisplenitis.
Chronic splenitis.

Acute conditions:

None noted.
No cultures taken.

Case IV.—D. I. H., 12162, Path. Lab. 1058. Woman, born 1834 (assigned date). Almshouse transfer. Delusions ("holy water taken away"), suspicious, visual hallucinations (talks to supposed faces), violence at night for unknown period before transfer. Committed August 31, 1904.

Malnutrition, teeth absent, edema of feet and lower legs, weakness of muscles, gait unsteady, slight tremor of hands, rather coarse tremor of tongue, vision defective, knee-jerks and Achilles jerks diminished, wrist and triceps brisk.

Disorientation for time (except month). Amnesia complete (could, however, repeat Lord's Prayer). Later complete disorientation.

Death April 24, 1906.

The autopsy showed *chronic conditions:*

Cardiac hypertrophy.
Chronic diffuse nephritis.
Sclerosis with calcification of aortic valve.
Mitral sclerosis.
Aortic sclerosis.
Coronary, basilar, and vertebral arteriosclerosis.
Chronic fibrous endocarditis.
Chronic fibrous pericarditis.
Chronic adhesive pleuritis.
Absence of diploë.
Chronic external adhesive pachymeningitis.
Chronic fibrous leptomeningitis (notably over vermis of cerebellum).
Pedunculated polyp of cervix uteri.
Hypertrophy of right lobe of thyroid gland.
Tumor (probably hypernephroma) of right kidney.
Diffuse cerebral atrophy.
Slight granular ependymitis of accessory sinuses of fourth ventricle.

Acute conditions:

Lobar pneumonia, bronchitis, and fibrinous pleuritis of right upper lobe.
No cultures taken.

Case V.—D. I. H., 12334, Path. Lab. 1103. Woman, born 1835. *Heredity:* Negative. *Personal history:* Diphtheria and scarlet fever as child. Bright scholar. Married, 1856. Two boys (both alive 1904); one miscarriage. Married again, 1874. Three or four children. Widowed, 1894. Tailoress till 1903. Corneal thickening of left eye began 1894. Gave up work on account of impaired vision. During 1904 absent-minded, gradually increasing amnesia, visual and auditory hallucinations.

Committed to D. I. H., 1904. Senile skin, slight anemia, teeth poorly preserved, muscular weakness, slight incoordination of finger movements, coarse tremor of tongue, vision absent in left eye and impaired in right, hearing defective. Died October 21, 1906.

The autopsy showed *chronic conditions:*

Emaciation.
Aortic sclerosis with calcification and ulceration in distal half.
Sclerosis of coronary, renal, carotid (expecially distal extremities of internal carotid) arteries.
Mitral sclerosis.
Cicatrices and local ulcerations of ileum (perhaps tuberculous, but not proved).
Chronic adhesive pleuritis.
Chronic diffuse nephritis.
Old scar and local fibrosis of liver.
Cholelithiasis.
Calvarium thin.
Chronic internal hemorrhagic pachymeningitis (right).
Diffuse cerebral atrophy (masked by edema).

Acute conditions:

Lobar pneumonia.
Hematoma of right side of scalp.
Bruise of face.
Cultures from blood and cerebrospinal fluid showed streptococcus pyogenes.

CASE VI.—D. I. H., 13442, Path. Lab. 1123. Woman, born 1832. *Heredity:* Father died of tuberculosis at 35. Mother died of old age over 80. One sister became melancholy after loss of four children and died in this condition at 75. Five brothers and two sisters normal, lived to old age. *Personal history:* Normal child. Common school education. Shoe-stitcher of fair capacity. Unmarried. Ceased mill work 1885. After 1885 occasionally nursed for small fees. Gradual physical failure since 1887 (then aet. 55). In September, 1906, worried over selling of relatives' house. Later insomnia, visual and auditory hallucinations, confusion lasting a week. Similar episode in October. Again in January, hallucinations, confusion, delusions of poisoning, disorientation for time, place, and persons.

On commitment, January 4, 1907, senility, vision defective, tremor of tongue, lips, and hands, muscular weakness, slurring and stumbling speech, radial and brachial arteriosclerosis, pulse 120, weak and thready, heart enlarged, organic reflexes defective, amnesia for both recent and remote events, complete disorientation, diminished impressibility. The temperature rose from 99° on entrance to 101° evening of January 8, and to 103° evening of January 14. Death January 15, 1907.

The autopsy showed *chronic conditions:*
Emaciation.
Brown atrophy of heart.
Mitral and aortic valvular sclerosis.
Chronic fibrous endocarditis.
Aortic sclerosis.
Coronary, pulmonary, carotid, and basal cerebral arteriosclerosis.
Small saccular aneurysm of right middle cerebral artery.
Chronic diffuse nephritis.
Chronic gastritis.
Chronic adhesive pleuritis.
Uterine polypi.
Calcified lymph nodes in perirectal tissue.
Hemangioma of liver.
Chronic fibrous pachmeningitis.
Diffuse cerebral atrophy.
Acute conditions:
Bilateral bronchopneumonia with acute bronchitis and lymphnoditis.
Acute splenitis.
Acute typhlitis and colitis.
No cultures were taken.

CASE VII.—D. I. H., 13358, Path. Lab. 1134. Woman, born 1840. *Heredity:* Unknown. *Personal history:* Largely unknown. Attack said to have been gradual in onset; 9 months before admission, about one year before death. Alcoholism probable. Disorientation, vagrant tendency, delusions of suspicion, wandering talk. Emaciation.

On admission feeble, senile skin, arcus senilis, left eye enucleated, cataract of right eye, enlargement of finger joints. Radial arteriosclerosis. Gait tottering. Slight tremor of hands. Brisk knee-jerks and Achilles jerks, plantar reaction slight, abdominal reflexes absent. Delirium and restlessness, with occasional attempts to walk about. Visual hallucinations probable. Was able to obey a few simple directions. Few relevant replies could be obtained. Amnesia for recent events complete; a few isolated facts from past life were recalled.

The patient remained completely disoriented for time, place, and persons; but her attention improved somewhat during the first week after admission. Motor restlessness occasionally appeared during December. Reactions occasionally suggested auditory hallucinations.

Death January 15, 1907.

The autopsy showed *chronic conditions:*
Emaciation.
Carcinoma of pylorus with metastatic nodule in stomach wall.
Brown atrophy of heart muscle.
Chronic fibrous endocarditis.
Aortic and mitral valvular endocarditis with calcification.
Aortic sclerosis with calcification.

Coronary, pulmonary, basal cerebral (including primary branches), splenic, and renal arteriosclerosis.
Slight hydropericardium.
Scars of left apex.
Bilateral chronic adhesive pleuritis.
Chronic splenitis.
Superficial fibrosis of liver, mesentery, and peritoneal wall.
Left eye absent.
Thyroid small.
Irregularity in thickness of calvarium.
Chronic fibrous pachymeningitis.
Diffuse cerebral atrophy.

Acute conditions:

Bronchopneumonia of right lower lobe with lymphnoditis.
Central necroses of liver.
Culture from cerebrospinal fluid yielded *B. coli communis.*

Case VIII.—D. I. H., 14099, Path. Lab. 1262. Woman, born 1838. According to patient father died at 72 of asthma. Mother at 50 of pleurisy. Two brothers were still-born; one lived 3 weeks. One sister alive at 65. No insanity or alcoholism in the family. At school till 16. Orthopedic operation at Massachusetts General Hospital in 1854. Occupation, housemaid. Since 1906 at Lynn poor-farm. Noisy and troublesome, singing and screaming at night.

On admission emaciation, contractures of legs and right arm, radial sclerosis slight, prominent temporal arteries, pulse small, rapid, of low tension. Sensations adequate with rough tests. Left ankle-jerk and knee-jerk brisk. Plantar reflexes and right ankle-jerks not obtained. Deafness, facial muscles normal. Blind. Incontinence of urine and feces. Stereognosis for many objects good, but patient could not tell a cent from a quarter by touch. Amnesia for both recent and remote events. Memory somewhat better for remote events.

Death August 16, 1908.

The autopsy showed *chronic conditions:*

Emaciation.
Contractures of legs and right arm.
Brown atrophy of heart muscle.
Chronic valvular endocarditis.
Aortic and coronary sclerosis with calcification.
Chronic obliterative pleuritis (right) and adhesive pleuritis (left).
Healed tuberculosis of apices.
Generalized adhesions of peritoneum.
Cholelithiasis.
Chronic diffuse nephritis.
Chronic atrophic hepatitis.
Perforation of right tympanum.
Slight diploë.

Cysts and calcified nodules in both ovaries.
Diffuse cerebral atrophy.

Acute conditions:

Tuberculosis of lungs.
(Tuberculous?) ulceration of transverse colon.
Cystitis.
Sacral decubitus.

General Clinical Analysis.

SEX.

This series of eight cases happens to be composed throughout of women. This fact is in accord with previous experience in the type of senile case termed by Kahlbaum *presbyophrenia*. Systematists like Kraepelin, for example, mention the predominance of females in presbyophrenia, but fail to note any sex differentiation in other mental disorders of the senium (senile depressions, deliria, delusional insanities).

A peculiar fact looking in the same direction was the statistical point made two years ago by Mitchell and the writer,[4] viz., that the female brains accruing from a series of insanities developing in the sixth and seventh decades were more often atrophic (8 of 11) than the male brains (5 of 12). As we then pointed out, the average age at onset of the females (58.4 years) was not much different from the male average age (59.5 years). But the females survived after onset on the average 8.8 years, whereas the males survived on the average only 2.8 years.

Assuming (what has not yet been proved) that a large series of statistics would yield similar results, we should be confronted with the problem how to explain the remarkable viability of females presenting the clinical features of senile dementia and *pari passu* undergoing cerebral atrophy.

A large series of cases is strictly necessary for the solution of this problem. For the moment it is enough to call attention to the somewhat remarkable fact that of all the cases (42) agreed upon as senile dements at the Danvers State Hospital, 1904-8, there were eight cases which showed a relatively pure brain atrophy, and these eight were all females.

Heredity and Antecedent Factors.

The data concerning *heredity* are lacking in four cases. Two cases have no heredity of insanity, whereas two more have some taint (872, " father and two brothers senile dements "; 1133, " one sister melancholy after loss of children "). Two cases appear to have been born to asthmatic parents (mother of 872, father of 1262).

The history with respect to *antecedent factors* is unobtainable in three almshouse transfers. Alcoholism is probable in one case (1134), the same which showed pyloric cancer at autopsy. The onset in one case is somewhat doubtfully related with a fall four years before death (849), and in one case is more definitely related with a fractured thigh (872). This case of mental disease subsequent to fractured thigh is the case in which we have the best evidence of hereditary taint, in which also we have record of a melancholy disposition throughout life and delirium during fever at the age of 51.

In two cases it appears that there were no upsetting factors (1103, 1133).

It would be of the greatest interest if we knew what relation these conditions bear to the menopause, but the data are lacking.

The important antecedent factors (except heredity) may be briefly enumerated as follows, based in part on clinical history and in part on autopsy findings:

872. Always melancholy, delirious in fever at 51 (old double pleurisy), fracture of thigh at 74, marked general and coronary arteriosclerosis, scar of right apex, chronic Bright's disease, malnutrition, double cataract, deaf.

849. Fall at 82, gall-stones and chronic fibrous peritonitis, obsolete tuberculosis of both lungs, radial, brachial, basal cerebral (no coronary) arteriosclerosis, chronic Bright's disease, obese, blind in one eye, deaf.

1050. Varicose veins; coronary, splenic, and renal arteriosclerosis; chronic Bright's disease; heart hypertrophy; impairment of vision and hearing.

1058. Heart hypertrophy, edema of legs, chronic Bright's disease; aortic, coronary, and basal cerebral arteriosclerosis; thyroid hypertrophy; malignant tumor of right kidney; vision defective.

1103. Corneal thickening at 59, left eye blind and right eye defective at 68, hearing defective, chronic Bright's disease, gall-stones, scars and ulcers of ileum, emaciation.

1133. Physical failure after 55, business worry at 74; radial, brachial, coronary, pulmonary, carotid and basal cerebral arteriosclerosis, chronic gastritis, chronic Bright's disease, organic reflexes defective, vision defective, emaciation.

1134. Alcoholism, pyloric cancer, general arteriosclerosis; left eye enucleated, cataract of right eye; emaciation.

1262. Gall-stones and generalized adhesions of peritoneum, chronic Bright's disease, healed tuberculosis of apices, aortic and coronary arteriosclerosis, blind and deaf.

Social Factors.

The above histories appear at first sight to have little of importance in common. There is, however, certainly little convincing evidence that social factors play much part in the antecedents of these cases (even in Case 1133 the business worry seems to be part and parcel of the disease, as it set in long after the onset of physical failure). Whatever the causes of the brain atrophy, it seems that they cannot be social.

Defects of Vision and Hearing.

But, if social factors are wanting, it is not so certain that individual psychic factors play no part. It is remarkable that all eight subjects showed severe defects of vision, combined in five cases with considerable deafness. The hypothesis lies very near that some part of the mental picture must be related with these defects of the long-distance receptors. Opinions differ as to the capacity of such defects to produce insanity. Congenital or early defects of the sort notoriously fail to produce insanity. But may not acquired blindness and deafness become effective in producing insanity when other senile conditions coexist? The history of case 1103 might suggest this.

On the other hand, it might not be unreasonable to see in the blindness and deafness merely effects of the cerebral atrophy. This is possible, though it must be pointed out that the blindness in some cases was partly peripheral, originating in cataracts in some cases and in corneal thickening in Case 1103. Careful cortical study is essential in the solution of this problem. In any event, we may suspect that a vicious circle exists in these blind and deaf dements, such that by a process of diaschisis the loss of long-distance perceptions reacts unfavorably upon a mental life already damaged in a variety of ways.

Are there any further common factors in these antecedents? As in the case of heredity and social environment, so too in the case of vicious habits, infectious diseases, and malignant disease, we find no constant or common factors in this small series.

Relation to Manic-Depressive Insanity.

A specific question likely to be raised about any senile mental disorder is, have there been previous attacks? Should we align these cases with the manic-depressive group of Kraepelin? There is, I suppose, no à priori reason why a manic-depressive subject may not eventually succumb to cerebral atrophy. I am disposed to think, however, that the brains of such cases usually stand up well and that manic-depressive cases, when they reach the senium, will be found rather in the arteriosclerotic group or the "normal" senile group than in the group of atrophies now under discussion.

The present small group of cases is in some respects unsuitable for this purpose. 872 is possibly, if by no means probably, a manic-depressive case.

The problem has been approached in an interesting manner by the English Commissioners in Lunacy (1905 and 1907),[5] who have shown that, in 20,680 admissions to English and Welsh insane hospitals (1903), the cases of first and not-first attacks were distributed as follows:

	First Attacks.	Not-First Attacks.
All cases not senile dements	13,970	5,546
Senile dements	1,058	106

Making all due allowance for the inadequacy of data in these aged subjects, it would appear certain that senile dementia cannot be made to include a tremendous proportion of manic-depressive cases.

We are reduced, then, in the particular small group of cerebral atrophies here considered, approximately to one of two etiologies—either to inherited tendencies or to causes operating in some concealed fashion in or prior to the senium. Obviously too, these two factors—inheritance and certain senile or presenile agents—may coöperate to produce senile mental disorder.

ARTERIOSCLEROSIS.

Since our data are thus far neither for nor against inheritance as a factor, we must consider the most prominent senile condition with which we are familiar—arteriosclerosis.

It has been the fashion to ascribe senile dementia, or a great part of its phenomena, to cerebral arteriosclerosis. Perhaps this relations was first asserted most confidently in Forel's clinic, whence Nötzli in 1895[6] issued a monograph on senile dementia, without, however, offering microscopic confirmation of the gross relationship asserted. This subject is considered at length in the anatomical sections.

Five of our series showed palpable sclerosis of the radial arteries (one of these, 1262, in which the radial sclerosis was slight showed prominent temporal arteries). Two cases, 872 and 849, were markedly arteriosclerotic clinically, and these proved to show the most marked general arteriosclerosis anatomically.

Three cases gave little clinical evidence of arteriosclerosis, and three more were but moderately sclerotic clinically.

In short, it would be difficult to prove any close clinical relation between arteriosclerosis and senile brain atrophy.

It must be borne in mind, however, that no one of these cases failed to show anatomically a certain amount of arteriosclerosis. In accord with general experience, this sclerosis was of focal and irregular distribution, affecting some organs and sparing others.

The clinical lesson appears to be that neither the presence nor the absence of radial arteriosclerosis offers important clues to the presence of cerebral arteriosclerosis. Not even the presence of severe changes in the radial arteries, or the concomitance of brachial arteriosclerosis, will permit us to divine the degree or even the presence of arteriosclerosis affecting the smaller or even the larger arteries of the encephalon. The same relation holds between peripherally demonstrable arteriosclerosis and, e. g., renal arteriosclerosis.

GENERAL CLINICAL FEATURES.

From the etiological or genetic points of view, we have incidentally considered several general features of these cases, such as the *blindness* constantly present in some degree, coupled frequently with some *impairment of hearing,* the tendency to peripheral *arteriosclerosis,* etc. These findings may be unified as follows:

Our group consists of eight blind old women, who all presented characteristic signs of senility on inspection, having a senile skin, and, as a rule, also *arcus senilis,* being almost or quite toothless, and diffusely wasted or weak in the voluntary muscular system, and subject as a rule to general emaciation. In short, these subjects could scarcely be distinguished from so many old almshouse inmates, non-insane. Even the blindness would not serve as differentia, as it seems to be grounded in a variety of lesions in the different cases.

Upon further examination, we find no constant situation or degree of peripheral arteriosclerosis, and little agreement in the general characters of the pulse (tendency to increased rate in the more obviously sclerotic cases). The heart is not constantly enlarged, nor are there any constant features upon auscultation. The renal data have not been consistently worked up (partly by reason of difficult collection of urine), but the autopsies have shown always either a chronic diffuse nephritis or renal arteriosclerosis. No other metabolic phenomena have been thoroughly examined. There is certainly no obvious metabolic fault in these cases beyond that which may accompany senility.

Comparatively few signs of focal lesion were made out upon neurological examination:

872. Questionable paraphasia, organic reflexes defective, pupils non-reactive to light (double cataract).

849. Lingual and labial tremor, left knee-jerk, left elbow and forearm reflexes exaggerated, right leg held flexed and weaker than left, incoordination in foot movements, muscle sense in legs diminished.

1050. Not remarkable.

1058. Lingual tremor, tremor of hands, wrist and triceps reflexes brisk, knee-jerks and Achilles jerks diminished, gait unsteady.

1103. Lingual tremor, slight incoordination of fingers.

1133. Slurring and stumbling speech; lingual, labial, and manual tremor; organic reflexes defective.

1134. Slight tremor of hands, abdominal reflexes absent, knee-jerks and Achilles jerks brisk, plantar reaction slight, gait tottering.

1262. Left knee-jerk and Achilles jerk brisk. Right Achilles jerk and both plantar reflexes absent. Organic reflexes defective. Stereognostic sense impaired (?).

Thus, *tremors, absence* of certain *superficial reflexes, variations* in some *deep reflexes* (tendency to loss of leg reflexes), *defective organic reflexes,* alterations of *gait,* and occasional slight *speech* disorder characterized these patients. Correlations with the details of the protocols and with the microscopic findings has so far not shown adequate reasons for the majority of these clinical findings. 1058 and 1134 seem especially consistent with present neurological knowledge. An examination of the spinal cord in 1134 showed a slight bilateral (approximately equal) pyramidal tract degeneration, as evidenced both by the Marchi preparations and by the neuroglia reaction. This degeneration appears to have been due to the atrophy of the brain which showed "convolutions, except of orbital surface, markedly atrophic, and atrophy especially marked in the Rolandic, parietal, and superior temporal gyri." The Betz cells of both precentral gyri are reduced in number, but the survivors show both axonal reactions and satellitoses. From these findings it may be concluded that such reflexes as those of 1134 do not directly depend upon focal lesions due to arteriosclerosis, but many hang upon atrophic cortical changes, in some instances at least.

Upon the mental side, communication is often rendered difficult through the defective vision and hearing of the patients, and there may be a not unnatural lack of spontaneity in their total relations with the outer world. It is difficult to prove by coarse tests that there is any loss of peripheral sensory power beyond that in sight and hearing; nevertheless such loss or diminution may be suspected to exist.

There is at all events certainly a deficient impressibility or perceptual capacity in these patients, which, coupled with a characteristic incapacity to remember recent events, serves to narrow the mental life to a remarkable degree. Whether the disorientation for time, place, and persons, so frequently noted, is quite constant and inevitable, may be doubted. Perhaps the condition would be better described as *lack* of orientation, than as positive disorientation.

The amnesia for recent events is constant. Whereas memory for remote events is also frequently deficient, the amnesia for recent events almost always surpasses that for remote events. (One exception, 1050, was an almshouse transfer who had apparently never been able to read or write.)

Both as a consequence of deficient sensory and perceptual capacity and by reason of the marked amnesia for current events, the intellectual life is much reduced in volume as well as devoid of variety.

So far the description qualitatively differs only slightly from what one might expect in the aged, and many writers give the impression that they regard senile dementia as a kind of projection of senility, in which the features of senility will be found to a more pronounced degree.

What is the ground of commitment of these subjects to insane hospitals? In the first place, aside from the question of insanity, these patients are difficult to handle by reason of their muscular weakness, blindness, and deafness, and sometimes by reason of disorder of organic reflexes. Strictly speaking, all these features of the disease could be handled outside of insane hospitals. Possibly 1050 was a case not, in the strict medical sense, insane.

Delusions were made out in four cases (fear of death, "holy water taken away," poisoning, suspicion), but occupy no prominent place among the symptoms.

Hallucinations or *illusions* were demonstrably or probably present in five cases at some stage. One case had before commitment many frightful dreams. The hallucinatory phenomena were as a rule visual or auditory or both, and it is difficult to say whether peripheral or central activity was the more responsible for these findings.

The hallucinations are in part chargeable with bringing about the nightly restlessness and noise of some of the patients, but apparently only in part, since the same restless, noisy, troublesome characters are exhibited by other non-hallucinated patients.

The most constant feature in these patients aside from the exaggerated senile features above enumerated, is *motor excitement.* This was present in all but two cases (1050 and 1103). Restlessness and screaming or howling at night are characteristic. The patients have spells of motor restlessness, alternating with quiet periods. The violent movements and noisy shouting are apt to come on suddenly and to quiet down gradually. During the spells patients are resistive. The garrulity of old age was exhibited in 1050 only.

AGE, ONSET AND DURATION IN ATROPHIC CASES.

	Age at Onset.	Character of Onset.	Duration.	Age at Death.
872	74	gradual, after thigh fracture.	7	81
849	81	gradual, after a fall?	4	85
1050	70	unknown	2+	72+
1058	61	unknown	2+ +	63+
1103	69	gradual	2	71
1133	74	gradual	¼	74
1134	66	gradual	1	67
1262	68	unknown	2	70

GROSS ANATOMY OF THE BRAIN.

The pia mater was normal or approximately normal in 5 of 7 cases in which its condition was noted; but in case 1058 it showed a slight diffuse fibrous thickening especially well marked over the vermis of the cerebellum, and case 1262 showed a few small opaque-white spots over the sulcal vessels. There was a well marked compensatory edema of the pia mater in six cases, but in one case, 1103, four days post-mortem, the brain substance had become soft and inelastic and had apparently imbibed most of the pial fluid. The basal cerebral vessels showed sclerosis in five cases; in one of these the sclerosis was confined to the basilar and vertebral arteries. One case showed involvement of the distal extremities of the internal carotid arteries, and in another case only one spot of arteriosclerosis was found in the entire brain, in a secondary branch of the circle of Willis. One case (849) showed a remarkable small varix in the right calcarine region noted and carefully studied by Prof. Barrett.

The brain weights are considered below in a separate table with comparative weights of other viscera. The convolutions, despite the assigned diagnosis of diffuse cerebral atrophy, do not show in all cases a perfectly even wasting. Thus case 872 showed more marked wasting in the upper left central convolutions. The anterior parts of the brain of case 1058 as far back as the precentral gyri were firmer than the superior parts, and the superior surface was firmer than the inferior surface. This case also showed a slight granular ependymitis of the accessory sinuses of the fourth ventricle. In two (recent) cases it has been noted that the orbital gyri failed to show as much atrophy as the other convolutions. These two cases also showed more marked atrophy in the central and parietal regions than elsewhere. Adjacent to the central and parietal regions of atrophy, case 1133 showed atrophy involving also the frontal gyri, whereas case 1134 showed atrophy more marked in the superior temporal gyri.

The consistence of the brain was firm or increased except in two cases in which the substance was soft, moist, and with diminished elasticity. In one of these no cultures had been taken, but the patient died of lobar pneumonia; in the other (also a case of lobar pneumonia) both blood and cerebrospinal fluid showed streptococcus pyogenes.

Evidence For and Against Arteriosclerosis as a Cause of Senile Dementia.

Nötzli[6] distinguished the psychoses of the senium into two groups: those without either focal symptoms or focal brain lesions and those with focal brain lesions. The focal brain lesion group was subdivided by Nötzli into two divisions *a:* cases in which there were never any focal symptoms or in which focal symptoms supervened late in the dementia; and *b:* cases beginning acutely with strokes or other focal symptoms.

Nötzli dealt with 70 cases. Of these 70 there were 40 cases without either focal symptoms or focal brain lesion.

The following table has been constructed from Nötzli's data to show the distribution of symptom groups in his 70 cases:

	Without focal symptoms.	With latent focal lesions.	With focal symptoms.
Senile Mania	6	..	1
Senile Melancholia	10	3	..
Senile Delusional Insanity	4	2	2
Senile Hypochondria	1	..	..
Dementia Alcoholica senilis	6	1	2
Typical Senile Dementia	13	9	10

Nötzli believes that in the group of senile mental disorders that we can distinguish two clinically different kinds. On the one hand a quiet senile dementia found most frequently in almshouses and nursing asylums, in which the dementia progresses slowly and quietly without periods of excitement. On the other hand diseases which resemble the diseases of adult life having frequently an acute onset and rapid course. Nötzli believes with Forel that the cases of the second kind (found in insane hospitals rather than in almshouses) are very probably of hereditary origin. He believes that cases of quiet senile dementia much more rarely show an inherited disposition to mental disease. In addition to the hereditary mental factor in the acute excited cases, Nötzli hypothecates a hereditary disposition to arteriosclerosis and particularly to cerebral arteriosclerosis.

The fundamental cause of senile dementia is in Nötzli's view cerebral arteriosclerosis and the often considerable atrophy of the brain conditioned thereupon, both in those cases in which atrophy is simple and in cases complicated by focal hemorrhages of softenings. The brain weight was found to be diminished on the average 200 grams and in such wise that the female brain preserved its normal proportion to the male brain in weight. The cerebral cortex was determined by separate weighings to diminish more than the other parts of the brain.

The evidence which Nötzli actually brings as to the relation of cerebral arteriosclerosis and cerebral atrophy is logical rather than histological. He regards all his cases as showing a combination of both processes and answers the question which is primary, as follows: It is well understood that the brain is also affected in the general physiological involution of the organism in old age. The brain is atrophied physiologically, to what degree cannot be expressed in figures, but simple cerebral atrophy can scarcely reach so great a degree, that is to say, yield on the average so low figures for brain weights as Nötzli's series of 70 cases showed. The cause of this atrophy of high grade must rather be sought in cerebral arteriosclerosis which places the brain under such unfavorable nutritive conditions as to cause it to atrophy in greater degree and more quickly.

The cerebral disease process is regarded as a purely degenerative one and as comparable to arteriosclerotic contracted kidney.

It is unwise to conclude that the changes of Nötzli's first group are all based upon nutritive brain disorder due to cerebral arteriosclerosis. Three protocols are presented. Case 34 was a physician 67 years old. It showed thickening and opacity of pia mater, superficial convolutional atrophy, atheroma of basal arteries, extreme dilatation of posterior cornua of ventricles, moist and anemic brain substance and extreme degeneration of the fine cerebral arteries with a brain weight of 1468 grams, the largest in the whole series of 70 brains.

Case 39 was a butcher of 64 years. It showed thickening, opacity, and edema of pia mater, moderate atheroma of basal arteries, extreme atrophy of brain, dilatation of ventricles, the left hemisphere was smaller than the right and the left corona radiata harder than the right. The left corpus striatum, thalamus, and corpus candicans much smaller than right. Cortex 1½ mm. deep on the right; on the left still narrower in many places. The total brain weight was 1044 grams.

Case 40 was a maid-servant 59 years old. Pia mater thickened and opaque. Basal arteries atheromatous. Brain atrophied; convolutions narrowed; convolutional surfaces irregular with groups of small degenerated arteries in some places. Focal atrophy of the left temporal lobe; left insula and left Broca's area thinner than right. Hydrocephalus. No cysts of softening. Brain weight 1106 grams.

Microscopic examination was not carried out in these cases.

Meyer[7] published in 1896 the data of 24 autopsies in senile dements from the Illinois Eastern Hospital for the Insane at Kankakee. Meyer reports that "in most instances there was undoubtedly atrophy of the convolutions present." The weights ranged from 942 to 1562 grams (weight taken "dissected," that is, minus membranes and ventricular fluid) and from 1025 to 1667 grams undissected. The majority of Meyer's cases have no assigned weights, and he shows in an instructive brief table of eight brain weights determinations how important a factor the dissection of the brain is in altering data. In the analysis of Meyer's data we must, therefore, rely rather on qualitative findings, and the grouping of cases is, so far as can be determined by analyzing his data, as follows:

MEYER'S KANKAKEE CASES.

Senile dements	24
Sclerosis of cerebral end-arteries	11
Brains atrophic, not arteriosclerotic	6
Brains not atrophic, not arteriosclerotic	7

No endeavor is made by Meyer to consider clinical data with the autopsy notes. In 23 cases with trunk dissection, Meyer noted " as an almost uniform feature on affection of the heart and the circulatory apparatus at large." For example " atheroma of the large blood vessels with hypertrophy of the left ventricle occurred fifteen times." " In only one case the organs of circulation were relatively normal."

The proportion of cerebral arteriosclerosis is treated as follows: " The blood vessels of the brain did not show any macroscopic lesion in the two youngest cases and none are noted in "(another case, a woman of 72)." A fourth case showed slight changes. " In all of these cases there were, however, found beginning atheroma of the aorta, slightly cystic kidneys, and in the two latter ones slight atrophy of the brain; 18 cases had marked atheroma (of the aorta); six of them very advanced calcifications. There has not been a single case observed in which alterations of the blood vessels could be excluded. Most of the other findings can be indeed traced to trophic changes."

Although Nötzli's conclusions with respect to the relation between cerebral arteriosclerosis and senile dementia are quoted, Meyer himself draws no conclusions in his report.

Appeldorn[8] from Schuchardt's Clinic in Rostock published in an inaugural dissertation in 1908 an analysis of 126 cases of insanity arising after the sixtieth year (817 per cent of the admissions to the Mecklenburg Asylum at Gehlsheim, 1897-1906) and among these considers especially 69 cases of what he terms typical senile dementia (not including senile melancholia, senile confusion, and other special forms).

Thirty-two of Appeldorn's cases came to autopsy, and, although the protocols are presented in too condensed a form, it appears that only 13 received or should legitimately receive the diagnosis of cerebral atrophy. Cysts of softening or very extensive arteriosclerosis are noted in but five cases, although the diagnosis of arteriosclerosis is set down without further specification in numerous other cases.

Appeldorn's data are far too sketchily treated to admit generalizations, and he contents himself with repeating the commonplaces of recent years on this topic. Whereas *Altersschwachsinn* depends on "simple physiological involution of the brain," *Altersblödsinn* or senile dementia depends on a pathological degeneration, eventuating in brain atrophy of much greater degree than that of physiological involution. Appeldorn cites Nötzli's hypothesis of the arteriosclerotic origin of senile dementia, but quotes with favor the hypothesis of Alzheimer concerning ganglion-cell changes of non-vascular origin. Finally Appeldorn agrees with Kraepelin that vascular disease is not extremely prominent in senile dementia and that extremely prominent vascular disease may not lead to insanity at all.

RATIOS OF ACTUAL TO CALCULATED WEIGHTS OF BRAIN, AND HEART, LIVER, AND KIDNEYS.

Autopsy number.	Sex.	Age.	Actual brain weight. *Calculated.**	Ratio.	Actual weights heart, liver, kidneys. *Calculated.**	Ratio.
872	F	81	$\frac{1180}{1121}$	1.05	$\frac{1280}{1499}$	0.85
1058	F	63†	$\frac{1070}{1212}$	0.88	$\frac{2840}{1818}$	1.5
1133	F	74	$\frac{990}{1121}$	0.88	$\frac{1735}{1562}$	1.11
1134	F	67	$\frac{980}{1194}$	0.82	$\frac{1465}{1740}$	0.94
1262	F	70	$\frac{950}{1190}$	0.79	$\frac{925}{1670}$	0.55

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* From data in Vierordt's *Daten und Tabellen*, Dritte Auflage, 1906, S. 40 usw.

† Very probably too low. In case the patient was 70, the figures run

$\frac{1070}{1190}$ 0.89 $\frac{2840}{1670}$ 1.70

The above table represents a fragment of some work undertaken by Mr. N. S. Burns * and myself to learn whether brain weights vary in the same or opposite directions with certain visceral weights. The general results of this work will be presented elsewhere. It will be seen that in this series the loss in brain weight varied from 21 per cent to 12 per cent, except in one instance where a gain over the calculated weight was registered. This gain was, however, only five per cent, which is almost within the limit of technical error as calculated by Mr. Burns and myself (data not yet published) ; so that at best this brain could be placed in the group of brains "normal" as to weight. As a matter of fact the surprising weight, in the presence of undoubted macroscopic and microscopic signs of atrophy, is perhaps best explained as a result of terminal infection (aureus sinus disease).

Leaving out the excess weight case, the brain weights are observed to vary with the visceral weights in two cases, against those in two others. The two cases in which the trivisceral ratio (as we have termed the ratio involving heart, liver, and kidney weights) is in excess are marked cardiorenal cases.

I present these results not as settling the problem, but as demonstrating that the hypothesis held by many that brain atrophy is due to arteriosclerosis is a quite unsafe hypothesis.

As mentioned above (under the clinical analysis of the arteriosclerosis found), Nötzli's results have had much to do with this hypothesis, but I do not find, upon analysis of his monograph, that much in the way of proof is advanced.

Alzheimer, 1898,[9] leaves in doubt whether senile brain degeneration is due to arteriosclerosis alone, and raises the question whether primary atrophic processes in the nerve cells may not be the true factor.

ARTERIOSCLEROSIS.

No case of our series escaped arteriosclerosis completely. Nor would it be wise to exclude this factor from the chain of events culminating in brain atrophy. It seems to me doubtful, however,

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* Working in the fourth-year elective in neuropathology, Harvard Medical School, 1908-9, holding an appointment as special laboratory interne, Danvers State Hospital.

whether the coexistence of these two conditions is a very strong argument for their causal relation. One prefers the non-committal position that both visceral atrophy and arteriosclerosis are conditioned upon some more remote cause, as yet unknown. It is certainly impossible to compare the degree of atrophy with the degree of arteriosclerosis, whether general or local. The distribution is as follows:

Arteriosclerosis generalized and marked	5
Aortic sclerosis	7
With calcification or ulceration	5
Coronary	7
Extensive or with calcification	2
Splenic, especially noted	2
Renal, especially noted	4
Basal cerebral	5
Internal carotid (not basal cerebral)	1
(Small aneurysm, right Sylvian artery	1)

The apparent sparing of the aorta in one case is probably due to an error in the protocol. On the other hand the immunity of the coronary artery in one case was expressly noted.

A tendency to cardiac or cardiorenal disease was observable in many of the cases. The occurrence of chronic renal changes is so constant that it would appear to me far more reasonable to look in the renal direction for factors in the production of brain atrophy than to look in the direction of arteriosclerosis.

HEART DISEASE.

Cardiac hypertrophy	2
Valvular disease	7
Aortic valvular	4
Mitral valvular	6
Chronic passive congestion of organs	4

KIDNEY DISEASE.

Chronic	8
Diffuse	7
Arteriosclerotic	1
Acute	1
(Cystitis	1)

Other Chronic Conditions.

Findings suggestive of tuberculosis, as a rule obsolescent, occurred in six cases, and can scarcely be excluded with safety from any case. This fact may easily be a coincidence, but the proportion is far higher than in most similar large *routine* series of examinations.

Other chronic conditions occurred in considerable variety and need not be summarized here.

The Cause of Death.

Lung disease was prominent in lethal factors (six cases, perhaps seven). The immediate cause of death cannot be exactly stated for all cases, but the positive indications of all properly examined cases are that bacterial infections are found in various loci (not always septicemic) with practical constancy. Thus it will be exceedingly difficult, for histological purposes, to procure an atrophic brain which can be trusted not to show acute effects. And, in a larger hygienic way, it is obvious that the better the nursing conditions, the longer these patients may be preserved.

Discussion and Microscopic Analysis.

I believe that the time is not ripe for a proper analysis of the cytology of senile dementia. In point of fact, no one can yet state precisely in what old age consists, so that our normal control pictures are lacking.

One of the most striking features of old age is the progressive loss of watery constituents which several of the tissues exhibit. Nowhere is this more striking than in the blood, which according to some writers undergoes a genuine atrophy in old age. If this should turn out to be true, it might be difficult to explain the mechanism of senility on a simple cellular basis like that of Metchnikoff.

In fact it may remain impossible to explain senility either on the basis of Metchnikoff's ingenious hypothesis concerning phagocytes or on the earlier conception of a progressive failure in cell-multiplication.

When the body in senility undergoes a loss of weight affecting virtually all organs in the same proportion, it will naturally be difficult to assign the cause of such loss to any given cell-mechanism.

It is far more likely that some general tendency, e. g., a tendency to partial dehydration, underlies the process.

I believe that some light will be thrown upon this subject by statistical studies in organ weights. Mr. N. S. Burns, who has been working with me in this direction, has prepared a number of comparative tables which show that some cases exhibit differential loss in brain weight, as compared with weights of other organs, whereas in other cases all the weights fall off together.

The whole problem is, therefore, definably complex, and I feel that the communication of cases showing various degrees of neuronophagia without complete life-histories and without knowledge of special bacterial, toxic, or chemical agencies at work upon an organ like the brain will scarcely tend to clear the issue.

Granting that physiological brain atrophy occurs, how can we distinguish pathological brain atrophy therefrom? First, the loss, in weight is more marked in the latter. Secondly, the onset of the process may be premature. Thirdly, the progress of the atrophy, as distinguished by clinical observation, may be much more rapid. Fourthly, a group of cases will show differential loss in brain weight, whereas the other organs will maintain weight better.

Waiving minutiae aside for the moment, it appears that so-called senile dementia will break into several entities, into, first, a group of cases in which there is not at all a true organic dementia, but in which old subjects with normal brains become insane just as younger subjects do (*senile acute psychoses*) ; secondly, a group in which there is local cortical arterial disease (*arteriosclerotic dementia*) ; and thirdly, a group in which the brain has undergone pathological atrophy (*senile dementia proper, or atrophic dementia*). Personally, I feel that future work may show that the latter atrophic group will split up into two subordinate groups, (a) a group in which through some metabolic flaw or for some other reason, the brain suffers *pari passu* with the other major viscera, and (b) a group with differential atrophy of the brain, possibly due to a special toxin or inherited tendency. Naturally, I should not wish to exclude combinations of these conditions in given cases, but I hold that detailed analysis should be made, so far as possible, of cases showing these conditions pure.

For reasons stated in the discussion I have not attempted elaborate microscopic analysis of these cases, but will present a number of examples of photographs illustrating the atrophy in different areas in several cases. (For descriptions, see plates.)

The matter of *neuronophagia*[10] has been of special interest, and my analysis of these and analogous cases has proceeded far enough to show that there is abundant microscopic evidence of the occurrence of pigmented or fat-laden neuroglia cells ("satellite cells") about the nerve cells of many layers in the senile cortex. Metchnikoff's interpretation of these findings may be upheld as against Marinesco's, as least so far as Marinesco holds the view that nerve cells undergo a kind of pressure-atrophy due to the accumulation of satellite cells. The latter interpretation is certainly not supported by preparations which I have seen.

If any hypothesis as to satellite cell action upon nerve cells need be risked, it is rather that the satellite cells exert some kind of chemical action upon the nerve cells, analogous to that exerted by osteoclasts in dissolving bone. Metchnikoff himself places this process of osteoclasis in a class logically separate from the process of phagocytosis in other organs. In fact, the process of osteoclasis, like Metchnikoff's so-called "phagocytic" action of sarcoplasm upon myoplasm in atrophy of muscle fibers, is regarded by some as not a good case of phagocytosis (in the earlier and stricter sense of a process of ingestion and digestion of particles by cells).

On the basis of observations alone, certainly such tissues as those of this series of brains go far to lend weight to Metchnikoff's assertions. But, whether or not certain trophic changes in the nerve cells antedate the appearance of satellite cells, one is scarcely able to decide. I am inclined to the conception that such changes do antedate the appearance of the satellite cells. If this be the case, Bevan Lewis' interpretation of these cells as scavenger-cells would be preferable.[11]

I have noted with interest that in three of my cases the satellite cells preferred a location alongside the apical processes of the pyramidal cells rather than the more frequent position at the bases of the cells. The frequency of this picture leads to the conception that in these cases the apical processes are the first to undergo atrophy, and possibly at a time when the axone is maintained. Two of these three cases were the oldest in my series (872 age 81, duration of mental disease seven years; 849, age 86, duration of mental disease four years). The third case, however, was but 67 years old with an assigned duration of mental disease of but one year (1134). The other cases of my series showed no preferred location for these cells, except the ordinary basal position with accumulation along the sides next the base. I have, for the present, no explanation for this finding.

The microscopic examination shows that minor vascular changes are observable even in this material, chosen especially to exclude vascular changes. Nor is it impossible that research may demonstrate a connection between these changes and the nerve cell and fiber atrophy. I am not convinced, however, that any strict proof has ever been brought of a causal relation between the changes mentioned. Notably they do not run *pari passu.* Wide stretches of tissue exhibit atrophic changes without attendant vascular changes of any consequence.

My contention is not that general nutritive conditions, in part arteriosclerotic in origin, may not have a hand in brain atrophy. Such conditions may lead to brain atrophy, as perhaps to arcus senilis, loss of teeth, or the senile skin. My argument is rather that no evidence has as yet been brought that *local* vascular changes produce brain atrophy. I feel, too, that in the long run we must also look back of the vascular system for an explanation of senile atrophic changes in general, and that we deal here perhaps with conditions similar to those unknown conditions which underlie thymus atrophy or menopause changes.

Summary and Conclusions.

1. Forty-two cases unanimously diagnosed " senile dementia " at the Danvers Hospital clinics have been reviewed clinically and anatomically, with a surprisingly low general percentage of accuracy (66 per cent) where *either* cerebral atrophy *or* cortical arteriosclerosis or both were regarded as confirmatory, and with still lower percentages: (48 per cent) where cortical arteriosclerosis was considered essential and (38 per cent) where cerebral atrophy was considered essential for a correct diagnosis.

2. The 14 cases which showed neither cerebral atrophy nor cortical arteriosclerosis (with obvious damage to the cortical tissues) are cases which probably should not have been termed senile dementia, and perhaps more properly belong in a group of acute

psychoses or other mental diseases occurring in old age but not dependent on recognizable senile changes.

3. Of the residuum, it is clear that cases in which cerebral atrophy and cortical arteriosclerosis are combined are not suitable for exact study, and attention has been concentrated upon eight cases of relatively pure brain atrophy, regarded as representing more nearly genuine senile dementia than the arteriosclerotic cases, which should be classed under the head of organic dementia.

4. True senile or senile atrophic dementia includes 1) cases in which the loss in brain weight proceeds *pari passu* with a general loss of weight in the other viscera and 2) cases in which the loss in weight of the nerve tissues is differential.

5. The mental diseases of old age, therefore, include

- (a) mental diseases occurring in, but not characteristic of, old age;
- (b) organic dementias due to cortical arteriosclerosis;
- (c) senile atrophic dementias, attended with
  - (1) general visceral atrophy,
  - (2) differential atrophy of the nerve tissues.

6. Obvious suggestions for research in the two groups of senile atrophic dementias as above stated are that the phenomena of general visceral atrophy may depend upon general decadent agencies (dehydration?) and that the more differential atrophy indicates special metabolic flaws or toxic agencies.

7. Since such a grouping has not been hitherto rigorously borne in mind, it is not possible to state the clinical features of these cases in detail.

8. Taking the group senile atrophic dementia as a whole, we find all the eight cases female, without special indications of inheritance, with very various antecedent factors (social factors not prominent), all markedly defective in vision (though for a considerable variety of reasons), often defective in hearing, all subject to various degrees of arteriosclerosis (in some instances not clinically made out), all showing the characteristic external signs of senility, and all showing either chronic diffuse nephritis (interstitial type predominant) or renal arteriosclerosis.

9. Neurologically, the eight cases showed characteristically *tremors,* absence of certain *superficial reflexes,* variations in some

deep reflexes (tendency to loss of leg reflexes), *defective organic reflexes,* alterations of *gait,* and occasional slight *speech* disorder.

10. Psychiatrically, communication with the patients is difficult and impressibility or general perceptual capacity is deficient. The amnesia for recent events is characteristic and constant. The patients are perhaps *unoriented* rather than disoriented. Amnesia for remote events is also frequently present. Delusions are not prominent. Visual or auditory hallucinations (or illusions) characterized some cases. Motor excitement and nightly restlessness and noise are characteristic, though not quite constant, and are not in all cases certainly due to hallucinations. Garrulity was surprisingly uncommon in this group.

11. Anatomically the pia mater was in general remarkably free from chronic changes, and, as the condition of the vessels was the basis of selection of the cases, the vessels naturally showed nothing grossly beyond involvement of the larger or pipe arteries (basal cerebral arteriosclerosis). The cerebral wasting was not in all cases quite uniform. One case even showed a slight granular ependymitis. The consistence of the brain tissue was in general increased.

12. A high percentage of obsolete tuberculosis characterized the autopsies.

13. Aortic sclerosis is probably constant in these cases. Sclerosis of other vessels is frequent but variable. The constancy of renal changes is interesting.

14. The cause of death is pulmonary in many cases, and is perhaps in some way bacterial in all.

15. No intensive microscopic examination has been undertaken, as the object has been rather to define the group of senile atrophic dementias. The satellite cell findings are consistent with Metchnikoff's hypothesis concerning phagocytic processes in old age. It is believed, however, that cell and fiber changes are very probably primary and "neuronophagia" secondary, or at any rate that these processes run *pari passu.*

16. A few cases showed satellite cells preferring the apical cell processes rather than the basal regions of the pyromidal cells.

17. It is alleged that no convincing evidence has been brought of a causal relation between *local* vascular changes and diffuse senile nerve cell atrophy.

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DESCRIPTION OF PLATES.

The photographs are in each instance from material fixed in alcohol and stained in unimbedded sections according to the original Nissl methylene-blue method.

The magnification is approximately 50. The sections were approximately 20 μ thick.

Fig. 1.—Left superior frontal gyrus (about midway) in Case I, female, age 81. The dementia developed gradually after a fracture of thigh, age 74. The photograph demonstrates generalized atrophy possibly more marked in the suprastellate layers and most marked in the layer of medium-sized pyramidal cells. The absence of vascular alterations is striking.

Fig. 2.—Left paracentral lobule in Case II, female, age 86. The dementia in this case developed gradually after a fall, age 82. The photograph demonstrates generalized atrophy. Some irregularity in the process is indicated by differences in the reaction of the neuroglia in the subpial layer; the neuroglia reaction is shown to be of more recent and cellular type on the left side of the photograph.

Fig. 3.—Right superior temporal gyrus of Case V, female, age 71. The dementia in this case developed gradually, age 69. The photograph demonstrates generalized atrophy. Considerable neuroglia reaction is evident in the subpial layer. Some irregularity in the process is demonstrated

prominently in the external layer of large pyramids, most of which have, however, undergone atrophy or total loss.

Fig. 4.—Left calcarine region of Case V. The photograph demonstrates generalized atrophy with considerable neuroglia reaction throughout. A solitary cell of Meynert is demonstrable below. Numerous neuroglia cells are seen in many places between the nerve cells. These are perhaps most marked in the outer pyramidal layers.

Fig. 5.—The left hippocampal gyrus of Case VII, female, age 67. The dementia in this case developed gradually about a year before death. Nerve cell losses and some neuroglia replacement are obvious in most layers.

Fig. 6.—Lamina from the right cerebellar hemisphere of Case VI, female, age 74. The dementia in this case developed gradually a few months before death. The photograph demonstrates a narrowing of the molecular layer upon the laminar surface which is striking as compared with the maintenance of depth in the molecular layer of the sunken portions of the lamina. Corresponding with the marginal diminution of the molecular layer there is a conspicuous absence of Purkinje cells as well as a development of neuroglia cells in the Purkinje cell belt. The neuroglia cells of the molecular layer are in general probably somewhat increased in number. Nor is there a proper quota of Purkinje cells in the lamina as a whole. Despite this atrophic process the vessels of the cerebellum show remarkably little alteration.

FIG. 1.

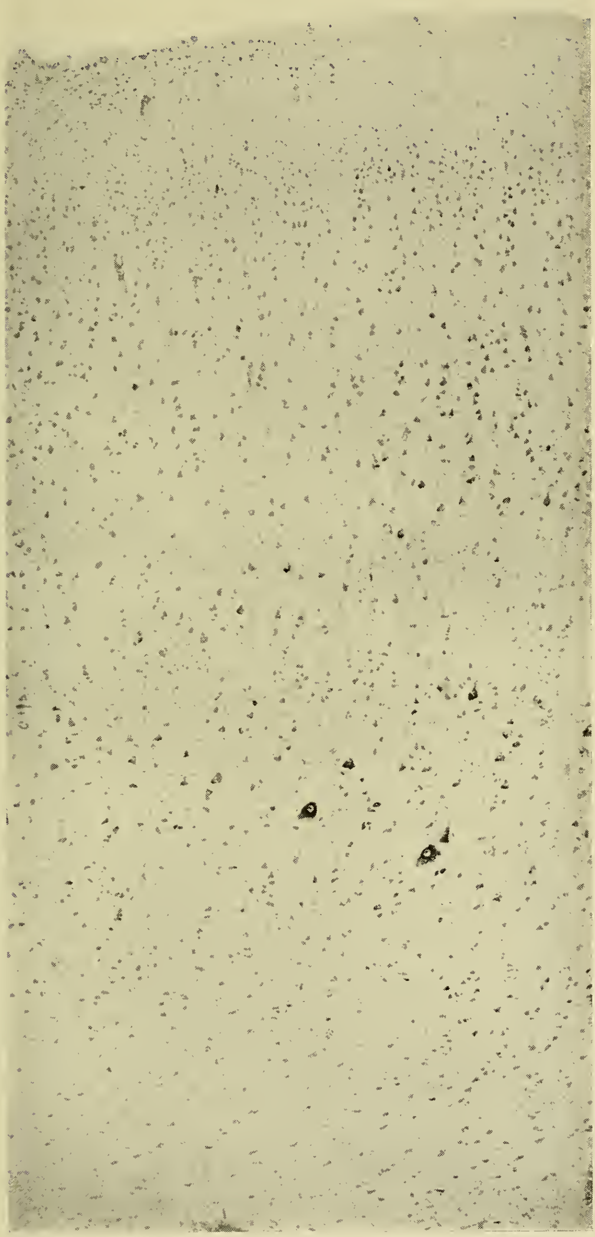

Fig. 2.

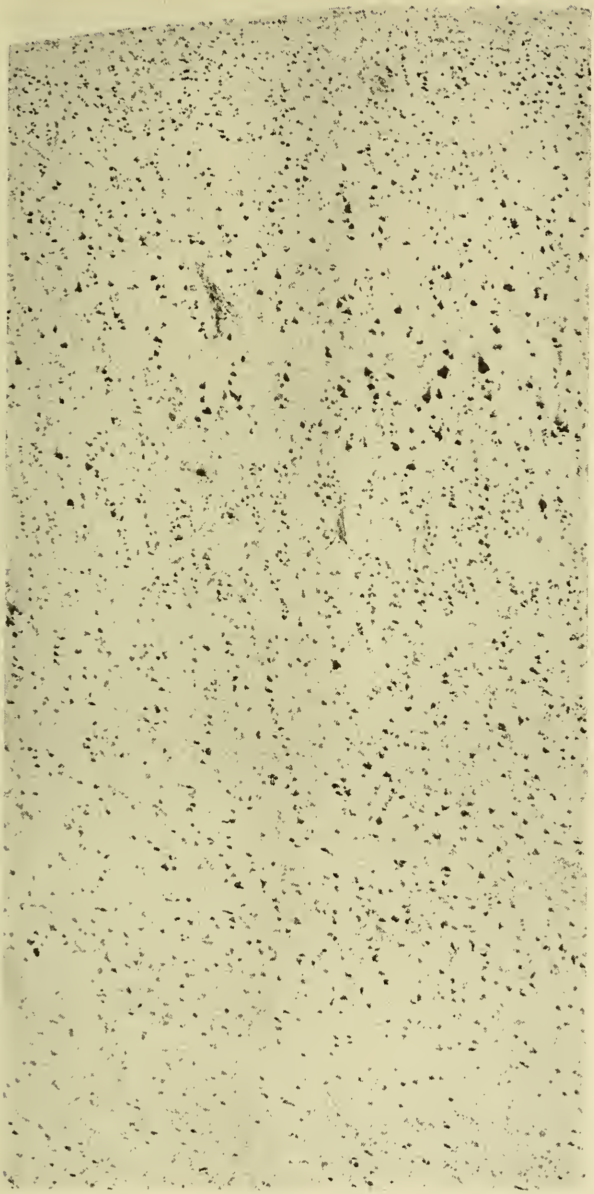

Fig. 3.

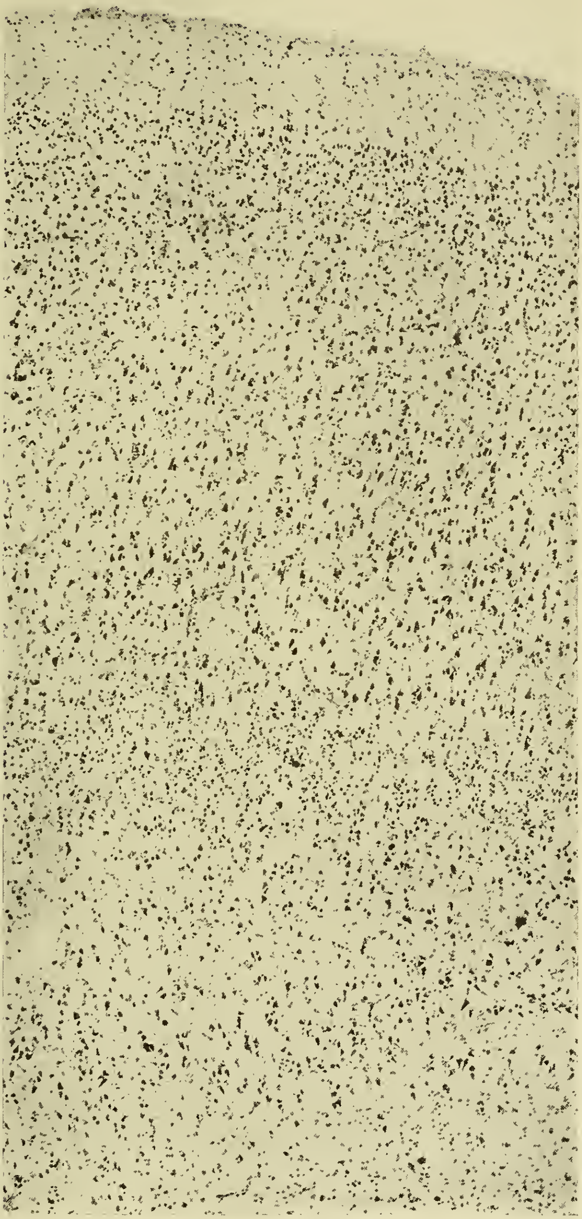

FIG. 4.

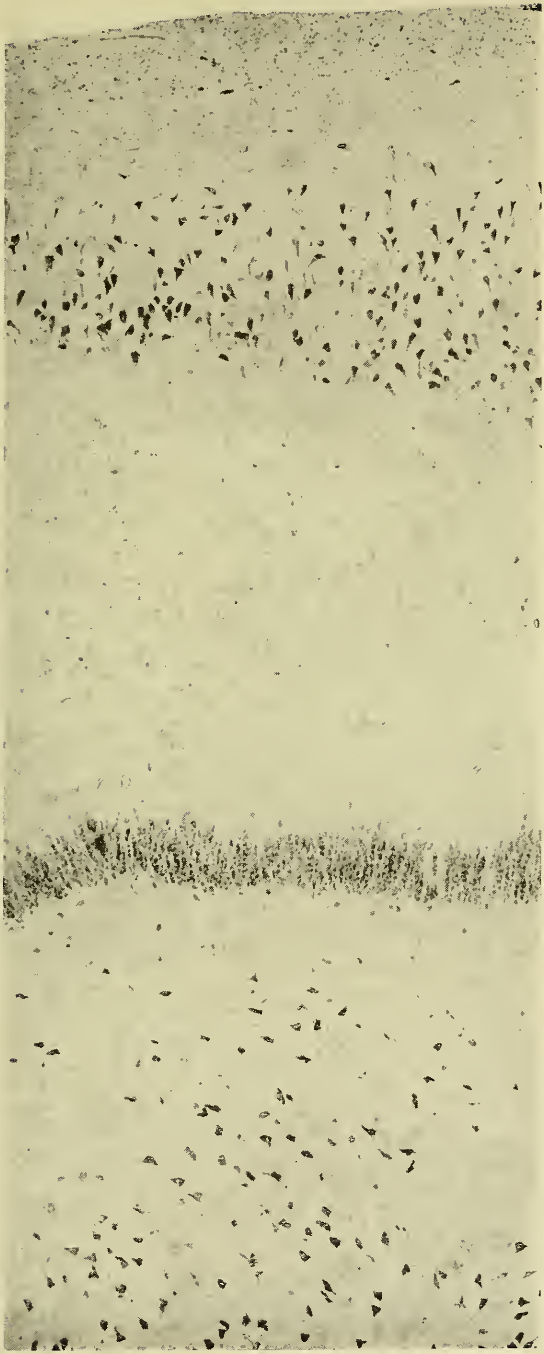

FIG. 5.

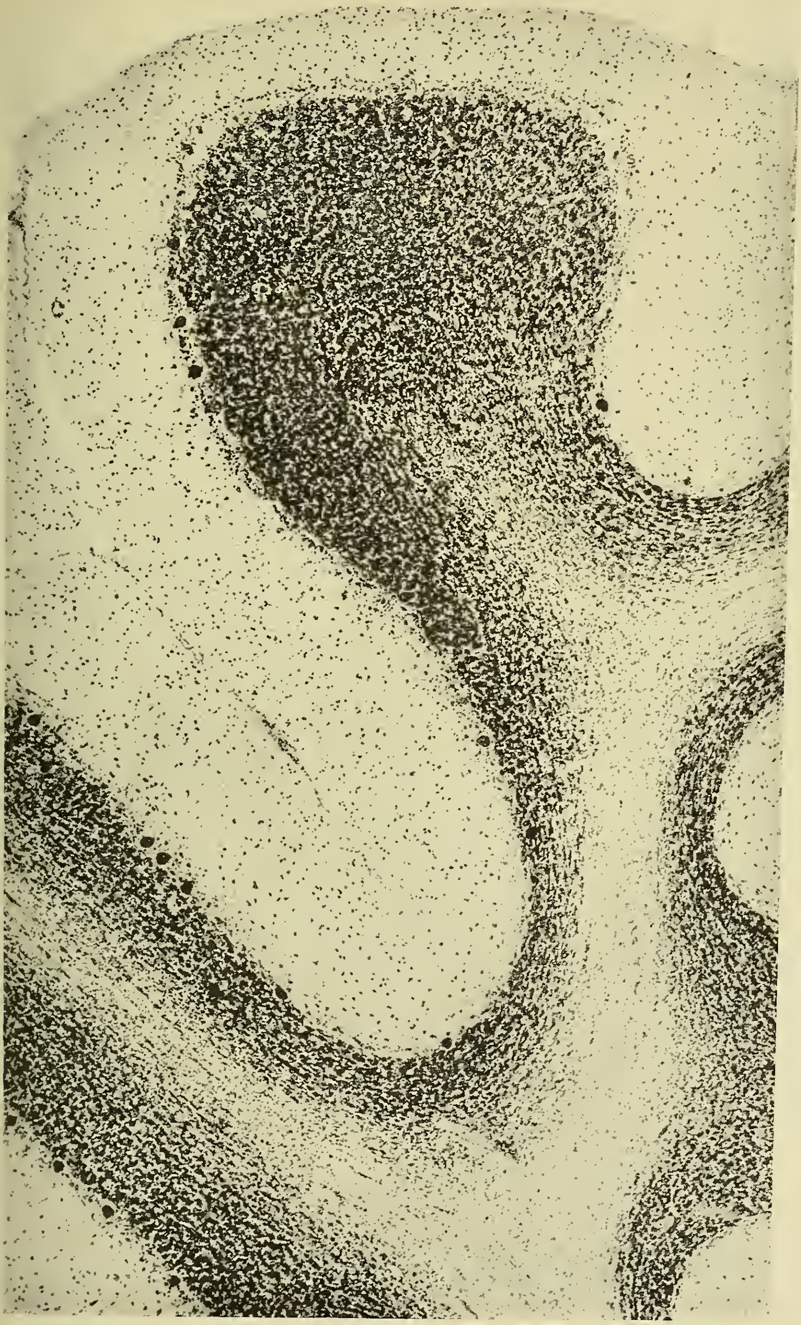

FIG. 6.

XXIV

DISCUSSION OF PSYCHIC AND SOMATIC FACTORS IN A CASE OF ACUTE DELIRIUM DYING OF SEPTICEMIA: NOTE UPON EXPERIMENTAL GUINEA-PIG INFECTION WITH STAPHYLOCOCCUS ALBUS.*

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IT seems worth while, in the present phase of discussion as to the causes of mental disease, to analyze closely every case which promises to demonstrate a *psychic*, as opposed to a *somatic*, origin. Especially important are those cases in which the data have been completed by death and autopsy. Although many psychopathologists feel that autopsies are of no particular service in their own campaign, it is probable that these men are in error, at least in so far as they disregard the possible effects of latent infection and metabolic flaws which autopsies more or less frequently indicate.

Two years ago a case of dementia precox was reported in this JOURNAL [1] (by Southard and Ayer) in which parallel analyses of the somatic and the psychic course of the disease revealed considerable doubt as to the proper interpretation of the case, i. e., whether it was somatogenic or psychogenic. The autopsy findings rather inclined one's judgment in favor of the somatogenic interpretation.

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* Read at the October, 1909, meeting of the Boston Society of Psychiatry and Neurology.

† Working in the Graduate Department of the Harvard Medical School (1908–9) under a grant from the Proctor Foundation.

Again, in the present case, we have attempted to present fairly both sides of the argument. We recognize the serious gaps in each of the parallel analyses. But, if the fundamental "complex" fails to appear on the psychic side, it is also true that many desirable somatic data remain dark.

I.

The *history* of the case is derived from the detailed and reliable observations of a physician who had known the patient well for many years, and from the records of the Boston State Hospital (due to the courtesy of Dr. Mary E. Gill).

The patient was a negress of Massachusetts birth, and thirty-six years old at the time of onset.

Family history. — There is a rumor, probably well founded, that mental disease had existed somewhere in the patient's family, but all details of this nature have been withheld by relatives. The patient's parents died when she was a child, but of unknown causes.

Personal history. — The patient was brought up in a cultured white family, by whom she was given a good education. It appears that the patient was a kind of companion in the house, and her patrons were attached to her because of her kindliness and good nature. No details of her life are available until her marriage, at about twenty-eight years of age. Her husband was a man about sixty years of age and is alleged to have married her so that she might take care of his declining years. Patient's husband was beyond the sexual age. The couple possessed some means, so that the patient never had to work for a living. The patient was accustomed to carry her husband's excessive age constantly in mind and, with the neighbors, harped upon the fact that, though she was provided for in a material way, her husband was not the man she had thought he was before their marriage. The patient was fond of children and helped her friends in domestic duties, such as sewing, at which she was exceptionally skillful.

Our informant often heard at intervals from various neighbors that the patient was complaining about the unsatisfactory character of her married life, but the patient never spoke of this to her physician, although she had been treated at various times for difficulty in menstruation due to retroversion.

Jan. 5, 1907, one year and six months before commitment to the Boston State Hospital, and one year and seven months before her death, the patient first complained of nervousness. It can be very definitely stated that this was the first period at which mental symptoms of any sort can have taken place during the years following 1900, as the patient was under familiar non-medical observation by our informant throughout this period. At this time the patient ascribed her nervousness to an upset due to the loss of a close friend by death. Again, after three weeks, the patient complained of nervousness, insomnia and a run-down condition. A third complaint dates from Feb. 11, 1907, and consisted of constant severe headaches, insomnia, constipation and nervousness. Sedative treatment relieved these conditions, and there was no further attack until August, 1907, when the headaches recurred. The notes of this date show that the patient recounted the dissatisfactions of her married life at length to her physician. The patient felt that moral strength was required to avoid breaking faith with her husband.

At no time prior to August, 1907, or until March, 1908, was there any suspicion of insanity in the patient, whose feelings and total reactions seemed quite reconcilable with her life and general attitude.

March 10, 1908, there was an enlargement in the posterior cul-de-sac, suggesting either gravid uterus or a tumor mass. On the hypothesis that the mass was a tumor, operation was advised, but this the patient refused.

May 10, 1908, the notes speak of eroticism and severe headache, and shortly thereafter the patient announced to the physician that she was going to get a divorce and marry a certain young man. In June, 1908, the patient complained of itching all over her body and was erotic in conversation and manner.

July 3, 1908, four days before commitment, she became acutely insane, running nude into the yard at her house, screaming loudly, and finally running several blocks to the house of the young man before mentioned. all the while shouting that God had spoken to her and that she had a vision and couldn't contain herself. She possessed the delusion that the young man before mentioned was divine and was induced to clothe herself in garments at his house, on the ground that these garments belonged to God. The patient then quieted down and related her hallucinatory experiences to the physician. She stated that God had permitted her to live with the young man to whose house she had repaired, that she had been told (in hallucinatory state) that he was a holy man, the Saviour. She said that she had been living with him for six months and concluded her story by stating that the Lord had told her that this young man was holy.

The next day the patient visited the physician's office and seemed quiet and somewhat improved. It appeared that for several days the patient had been, according to her husband, hyper-religious, reading her Bible the greater part of the day, contrary to custom. She had also, contrary to custom, neglected to rise and prepare her husband's breakfast. The patient explained her denudative impulses by stating that God had told her not to wear clothing.

It is possible that in some of these attacks the patient was confused, and it is stated that amnesia occasionally followed. There was never any violence or suicidal or homicidal tendency. Convulsions were lacking. The patient was somewhat negativistic, but could be reasoned with, especially if her delusions about God were humored. Just before commitment, July 7, 1908, the patient was in bed apparently in a dull and stupid state, but upon questioning expressed many of the ideas just sketched. Before admission the physician in charge noted a slight degree of swelling in the legs. This was not marked enough to be noticed by the hospital examiners, though both face and hands appeared somewhat puffy. The face showed considerable acne. The pupils were equal and contracted and are said to have been non-reactive to light (examination difficult in a colored subject). The knee jerks were equal but diminished. There were no other neurological alterations. The tongue showed a moist, heavy, white coat. The urine was negative.

Mental examination. — Consciousness appeared clouded and orientation for time imperfect. The date was stated to be June, 1900. Upon assurance that the date was 1908 she replied, " They say it is 1908 because they don't know their God," but later admitted that it really was 1908. The patient showed every objective sign of auditory hallucinations, sitting at times with eyes closed and not disposed to answer questions for some moments, later explaining that God was talking to her. She was occasionally interrupted in a remark by an hallucination.

During the next few days certain symptoms suggesting katatonia were noted, such as mutism, staring, drooling, resistiveness and assumption of a tense muscular attitude with acts suggesting uncontrollable impulses. The patient would at times sit with eyes tightly closed and appear confused, but would suddenly start up screaming and running about the ward.

July 18, fifteen days after the onset, it was first noted that the left leg was markedly swollen, though without evident discoloration and without deformity. The popliteal space was full and tender on pressure. The slight swelling of legs noted by physician before commitment had not interfered with locomotion and had not been observed in the hospital until this date. The patient was now confined to bed with a temperature of 101°. It is stated that she had at periods been very restless, screaming and resistive, and also showed catatonic stupor before taking to bed. The hypothesis was raised that the swelling was due to phlebitis, although there was no history of miscarriage or even of pregnancy.

July 21, 1908. The patient fell on rising from bed, but sustained no injury. Food was refused and patient was tube-fed. The patient was resistive and noisy at times.

Thereafter the patient became restless and lay tossing in bed with a delirium, with frequent moaning. The temperature never rose above 100°, and a somewhat unsatisfactory examination of the chest, Aug. 1, showed no pneumonia. Meanwhile the swelling of the left leg had almost completely subsided. Tube-feeding had been resorted to at intervals. Aug. 2, temperature 102, pulse of 100, poor quality. Pelvic examination discovered a large mass in front and on both sides of the uterus, stretching well up on the umbilicus. This mass had never before been made out, perhaps because of the resistiveness of the patient. On this date there was rigidity of the muscles and of the abdominal wall, but no tympany. Aug. 3 expert gynecological examination resulted in a diagnosis of multiple fibromyomata of the uterus. By this time the patient had become no longer resistive. The abdomen had become soft and the tumor easily palpated. The mental state showed delirium and patient took no notice of her surroundings. Restlessness and constant moaning. Nourishment was not taken; tube-feeding was difficult. Salt solution enemata were given. Neither heart nor lungs were abnormal. There were no râles. The peripheral circulation was sluggish. The left leg was little larger than the right and not especially tender. Aug. 4, temperature 103, pulse 106, feeble; respirations, 40. After lying quietly and moaning a little at intervals and saying nothing that could be understood, patient died, one month after onset.

In view of the autopsy findings given in detail below, and in view especially of the thrombosis of the vena cava and its branches, it is important to state that the swelling of the legs was at no time, except for a few days after July 18, extreme and was in fact variable in degree. Possibly, almost up to the last, the edema of the legs was largely due to the pressure upon the rim of the pelvis by the massive fibromyomata. There was at no time any clinical sign of the pulmonary thrombosis until the day before death. Further clinical analysis is given below.

II.

The *autopsy* was performed eleven hours after death by one of the writers (E. E. S.). Following are the

ANATOMICAL DIAGNOSES.

Thrombosis of vena cava, common iliac, external iliac and femoral veins.

Thrombosis of both pulmonary arteries.

Edema and congestion of lungs.

Bronchopneumonia of both lungs posteriorly.

Acute fibrinous pleuritis (left).

Ecchymoses of lesser curvature of stomach.

Injection of mucosa of rectum.

Multiple fibromyomata of uterus with occlusion of Fallopian tubes.

Corpora lutea and corpus hemorrhagicum.

Chronic pelvic cellulitis.

Dislocation of cervix uteri.

Acne and acne scars of chest, forehead, lips and chin.

Ecchymoses of scalp and pericranium.

Mitral sclerosis.

Aortic and coronary sclerosis.

Pulmonary valve, four cusps.

Chronic splenitis.

Acute nephritis.

Slight hydro-ureter (both sides).

Slight chronic leptomeningitis about optic chiasm.

The details of the autopsy are as follows:

Body, 151 cm. long; development and nutrition good; moderate rigor of extremities; moderate edema of both lower legs and thighs, approximately equal on the two sides. Acne and scars of old acne of chest, forehead, lips and chin. Pupils equal, 5 mm. Teeth show several fillings with gold. Abdomen slightly retracted. Firm mass palpable above symphysis. Neck bent to right. Subcutaneous fat of abdomen 3.5 cm. thick.

Peritoneal cavity: Walls moist; considerable venous injection posteriorly. Omentum long and thinly clad with fat. Appendix 8 cm. long, provided with mesentery throughout, attached to inner border of cecum and compressed by pelvic mass. Pelvis filled with smooth mass of fibromyomata (see below).

Pleural cavities: Left normal except for recent fibrin deposit over posterior border of lower lobe and over diaphragmatic surface. The lobes are united externally by recent fibrin. Right normal.

Pericardial cavity: Not remarkable.

Heart: Weight, 255 gm. Pulmonary valve, 8.5 cm.; aortic valve, 6 cm.; tricuspid valve, 11.5 cm.; left ventricle, 1.5 cm.; mitral valve, 10 cm.; right ventricle, .3 cm.

Heart muscle of normal appearance. Valves normal, except mitral, which shows faint patches of sclerosis remote from valve edge.

Lungs: Weight, left, 300 gm; right, 310 gm.

The pulmonary arteries of both sides show thrombi somewhat firmly attached at several points to the endothelium and extending into the primary branches. The thrombi are mixed red and gray, of friable consistence and closely molded to the shape of the arteries. The lungs contain no frank infarctions. The posterior part of both lobes of left lung is prominent and non-retractile, but fragments from all parts of lung float in water. The lowermost angle of left upper lobe shows a focus containing externally an abscess greenish in color, covered with fibrin, but on section the lung tissue is merely somewhat dryer than the remainder of lung and shows no point of suppuration. The right lung is almost wholly free from lesions, but shows slight edema and congestion posteriorly. Bronchi of left lung normal. Left lung slightly reddened. Bronchial lymph nodes small and black.

Spleen: Weight, 50 gm. Capsule slightly thickened. Substance of a maroon color, not pulpy, with Malpighian bodies not visible and showing a diffuse increase of interstitial tissue of moderate degree.

Gastro-intestinal tract: Esophagus normal. Stomach shows a moderate number of rugæ and is injected over the lesser curvature. Duodenum, jejunum and ileum contain semifluid material. The cecum contains a moderate quantity of formed feces. Large intestine otherwise normal, except for reddening of the tips of the folds in the rectum.

Liver: Weight, 950 gm. Border sharp, capsule smooth, substance plum-colored and well injected.

Gall bladder not remarkable.

Pancreas not remarkable.

Adrenals normal.

Kidneys: Weight, 200 gm. Strip readily; cortex well injected; markings distinct; radial opacities of both cortices especially distinct towards the intermediate veins, suggesting an acute process. Ureters both somewhat distended, but otherwise not remarkable.

Bladder normal.

Genitalia: The uterus is indistinguishably merged in a mass of fibromyomata, roughly oval in shape, with major axis pointing from the right above to the left below. The mass measures 13 cm. x 8 cm. x 9 cm. in diameter, and is composed of several large fasciculated masses, of fibrous appearance, which can be somewhat readily shelled out from loose fibrous capsules. The diameter of the uterus does not seem to be reduced in size. The mucosa is slightly reddened. The cervix is bent into a curve with the concavity anteriorly, by reason of the encroachment of long fibromyomata behind. Cervix contains a small amount of mucus. There are no scars upon the os; vagina normal. Attempts were made to pass probes from the uterine cavity through the tubes, but the lumina of these seemed occluded. The right fimbria is congested. Both ovaries contain corpora lutea, and the right contains a corpus hemorrhagicum. The left ovary is about half the size of the right and is bound down by adhesions. The pelvic cellular tissue is extremely firm and dense.

Aorta: Posterior surface of aorta shows a few faint patches of sclerosis. The coronary arteries show small early patches, and adjoining the sinuses of Valsalva are a few larger patches.

The vena cava: The lower 5 cm. of vena cava contains a mixed red and gray thrombus attached somewhat firmly to the posterior wall and continuous with similar thrombi of both common iliac, both external iliac and both femoral veins. The lower parts of the thrombi are looser in texture and are much admixed with post-mortem clot.

Head: Hair heavy; scalp shows a few ecchymoses over frontal region. There is a large spot of hemorrhage in the pericranium over left parietal bone, 2 cm. in diameter. Skull of normal thickness, but dense. Dura mater nowhere adherent to calvarium. Sinuses not remarkable. Middle ears normal. Nasal cavities normal. Pia mater well injected, especially in right hemisphere, both in sulci and over tips of gyri. Slight overgrowth of fibrous tissue over optic chiasm. Pia mater everywhere delicate and transparent.

Brain: Weight, 1,200 gm. Consistence throughout normal. Very few annectant gyri. Gyri in general symmetrical. Cortex nowhere shows on section a diminution in thickness. Substance is moister than normal. Cerebellum and pons: Weight, 145 gm. Superior surface of cerebellum extremely soft and without focal lesion. Ventricles show a normal ependyma. Interbrain and midbrain normal on section. Considerable pigmentation of pia mater and spinal cord in cervical region.

III.

At autopsy *cultures* were made upon agar plates from the heart's blood, the brain and a mesenteric lymph node. Both blood and brain yielded numerous colonies of staphylococcus albus, whereas the mesenteric lymph node culture remained sterile. (For these data and the organism, we wish to thank Dr. A. H. Peabody, assistant physician, Danvers State Hospital.)

Parallel with previous work in this laboratory,[2] numerous inoculations were made with the cultivated organism by several routes in guinea-pigs. Subcutaneous and intraperitoneal inoculations yielded no clinical sign of injury in the guinea-pigs. A series of injections of like amounts of the staphylococci, grown and suspended in bouillon, was made by way of the orbit, with the object of studying such phenomena of meningitis and encephalitis as might ensue. Animals were killed at intervals of three, six, nine, twelve, eighteen and twenty-four hours, at the end of two, three, four, five, six, seven, nine, eleven, fourteen and twenty-one days after inoculation. Cultures were made upon agar slants from beneath the forebrain after removal of the calvarium and lifting the brain with sterile forceps. Growths of the albus were obtained from this locus in the majority of animals of this series, beginning with the animal killed after twenty-four hours and ending with the animal killed upon the fourteenth day. Animals killed prior to twenty-four hours after inoculation consequently failed to yield organisms. (From one twelve-hour brain a single colony was obtained.) This work appears to confirm the impression derived from previous work that many types of organisms will grow through or be carried through from the orbital tissue to the meninges in the guinea-pig.

As a control upon the bacteriological examinations in this series, sections were prepared from the brains of a typical series of animals illustrating the various time intervals. The course of the inflammatory process as exhibited by leucocytosis, emigration of leucocytes and diapedesis of blood globules was shown to follow rather exactly the results obtained with cultures. No instances of emigration of leucocytes through vessel walls were obtained until an animal killed twenty-four hours after inoculation was examined. A few of the arteries in this brain showed excessive numbers of leucocytes, with accumulations of leucocytes outside the vessel walls and groups of cocci. The cocci were by no means habitually engulfed in the leucocytes. It was, in fact, unusual to find such evidence of phagocytosis. It is possible that in some instances the access of bacteria to the meninges from the orbit is more rapid than indicated, since in one animal, killed twelve hours after inoculation, blood and leucocytes were found in a few foci in the pia mater, especially beneath the cerebrum. From this brain (as stated above) a single colony of staphylococci had been cultivated; no bacteria were found in section.

The fastigium of the mild hemorrhagic meningitis, characteristic of these inoculations, probably occurs from the third to the fifth day and perhaps rather earlier than later in this interval. These results correspond with previously published results of aureus inoculations.[3] Mononuclear cells are not characteristic of these exudates, so that once more the parallel with aureus effects is maintained.[4]

As a control upon the histological study of the exudates, Marchi preparations were made from a representative series of animals. A large number of Marchi preparations were made, representing several areas of the nervous system, including the medulla and spinal cord, so that the occurrence of Marchi degenerations having possibly nothing to do with our inoculations might be observed. The necessity of such control work in all studies of Marchi degenerations outside the field of definite tract or systemic diseases has been emphasized by work done in this laboratory both on the nervous system of guinea pigs suffering from diphtheria toxone paralysis and upon guinea pigs examined in the course of work on anaphylaxis.[5]

It will be remembered that the Marchi degenerations shown in animals subject to inoculation with bacillus typhosus[6] appeared tolerably late in the ensuing disease, appearing in demonstrable amount about the seventh day and running behind the exudative process by some days. In the present albus series the brains and cords were negative or virtually negative up to two or three days after inoculation, when a very slight blackening in the fibers of the white matter in the cerebrum appeared. Thereafter little blackening was exhibited, except in an occasional bundle of fibers at the base of the brain. It is difficult to exclude experimental artefact for such occasional degenerations. The whole picture in this albus inoculation series is far less striking than in the typhoid inoculations.

IV.

The microscopic examination of the *organs of the trunk* served largely to confirm the gross diagnoses, but also gave evidence of several additional minor lesions.

Heart. Besides the slight coronary sclerosis revealed in the gross examination, the heart showed a few foci of mononuclear cells of the lymphocyte type in the fat tissue near small vessels, a minor degree of perinuclear pigmentation in the muscle fibers, a few trifling accumulations of fibrous tissue along trabeculæ, and little or no evidence of acute change.

Lung. In places, considerable edema without pronounced cellular infiltration; plugs of fibrin and leucocytes in some of the small veins; recent fibrinous pleuritis (section from left lung). A moderate number of phagocytic cells, as a rule containing blood, are found in the alveoli.

Liver. The liver shows an acute degenerative process, confined almost exclusively to the lobule centers. The cell columns here are narrow. There is a considerable free space between the parenchymal cells and the capillary walls, which is filled with granular material. The cell columns in these places are somewhat highly pigmented. The capillaries in the lobule centers are only moderately dilated. There is little or no evidence of acute exudation. The portal veins are all greatly distended.

Hypophysis. The vessels of the hypophysis are distended. There is considerable colloid deposit in some of the acini.

Otherwise the microscopic examination yielded no further points. It is interesting to consider the age of the thrombi. Sections from the pulmonary thrombi showed no evidence of ingrowth of connective tissue into the thrombi.

Gasserian ganglia. There is a mild diffuse chronic lesion involving a great majority of the ganglion cells, which are surrounded by a double or triple layer of capsular cells. There is no evidence of very acute cell destruction. A moderate chronic interstitial process accompanies the cell changes.

The *cerebral cortex* was examined in several areas and everywhere gives the impression of being but slightly, if at all, altered by disease.

The white matter everywhere presents the usual regular arrangement of neuroglia nuclei. The neuroglia elsewhere appears quite normal, save that in a few places, notably opposite pial veins, there is a slight fibrillary thickening of the subpial felt work; this change, if it be pathological, seems to fall logically into a class with the slight cerebellar changes noted below.

The vessels are only in places injected. There is little or no perivascular gliosis. There are a few pigmented cells in some perivascular sheaths in almost every region.

The nerve cell layers present the usual topography, and, although a certain number of "axonal" reactions were determined, there was little other evidence of acute change.

In a few regions were found small areas of fibrinoid change in parts of walls of small vessels, with groups of polynuclear leucocytes clustered near. In several places an accumulation of granular coagulum was found containing mononuclear (endothelial?) cells.

The *cerebellar cortex* is almost completely normal (specimens from each hemisphere). An occasional laminar tip shows a surplus of neuroglia cells in the Purkinje cell belt, but nowhere is there a frank loss of Purkinje cells. The cell elements of the granular layer are also properly maintained, except in a few small foci, where, for a half millimeter or so, some of the granule cells have been lost, as indicated by the drawing together of the eosin structures of Denissenko. No acute changes were demonstrated.

V.

Let us analyze the course of this case in two ways:

ANALYSIS I (PSYCHOGENIC).

Let us emphasize at first, so far as possible, the psychogenic features:

A well-educated negress, with probably some hereditary tendency to insanity, marries at twenty-eight an impotent husband of sixty. Six and a half years later she develops nervousness, insomnia, headaches, with considerable constipation. When seven years married the patient becomes free in recounting sexual dissatisfactions to her physician and begins to think of other men. Fifteen months after nervousness had set in there is discovered an enlargement in the uterus, which doubtless worries the patient much, though operation is refused. Thereafter headaches and eroticism are frequent symptoms.

Suddenly, eighteen months after the initial nervousness, four months after the first symptoms, which her physician was inclined to call symptoms of insanity, the patient develops acute insanity of a type not exactly definable, but perhaps best expressed by the term "acute delirium" (hyper-religiosity, auditory and possibly visual hallucinations, disrobing upon hallucinatory command of God, questionable episodes of confusion and amnesia). Death follows a month later from pulmonary thrombosis following pressure of massive fibromyomata upon the iliac veins.

ANALYSIS II (SOMATOGENIC).

Let us next analyze the case, emphasizing the somatic features:

A well-educated negress, with probably some hereditary tendency to insanity, marries at twenty-eight an impotent husband of sixty. Six and a half years later she develops nervousness and insomnia, together with headaches and constipation, which the subsequent history indicates are probably due to the growth of fibromyomata of the uterus. Meantime the patient complains at times of sexual dissatisfactions. The uterine growth, which only later was certainly diagnosed as fibromyomatous, becomes palpable fifteen months after the initial train of symptoms had set in. Whether the eroticism which now accompanied the other symptoms is at all conceivably due to impulses from the uterine region is doubtful. Operation is refused.

Acute insanity of delirious type (for details see above) develops, and the only physical symptoms then of note are acne and a slight swelling of the legs (observable by family physician, but not noted by examining physicians unfamiliar with patient).

Following the somatic symptoms, it appears that a marked swelling of the left leg, with fulness and tenderness of the popliteal space, was first noted in hospital fifteen days after onset, accompanied by a temperature of 101°. The swelling subsides to some degree later, so that it became difficult to say that one leg was larger than the other. It is hard to say at what time the iliac vein thrombi began to develop. Possibly the swelling of both legs, noted in the acute outburst, was due to pressure upon the veins by the fibromyomata rather than to the growth of thrombi within the veins. Also it is impossible to say when the septicemia began. Whether the septicemia developed prior to the acute outburst or fifteen days later, it remains certain that in the first fifteen days of the insanity there was evidence of an important somatic disease (massive fibromyomata exerting pressure upon the iliac veins), the results of which became later inextricably mingled with the mental symptoms.

DISCUSSION.

It is possible, by shifting the emphasis in a clinical history, to convey two quite separate notions as to the genesis of a given case of mental disease. Yet an answer to the question whether somatic or psychic (hereditary, individual, social) factors are the more important in many cases of mental disease would be decisive in the inclination of research upon these factors. It is our opinion that research should be inclined upon the side of the bacteria and the toxins in appropriate cases.

Although no single logical step in the process is absolutely safe, we feel that a reasonable account of our case might be as follows:

1. A cluster of nervous symptoms, compounded

from the effects of uterine growths and unhappy married life.

2. Latent blood infection (staphylococcus albus bacteriemia) possibly related, through some unidentifiable atrium of infection, with acne.

3. Rapid and massive enlargement of uterine growths (determining in some obscure way the sexual trend of symptoms?) and pressure upon the iliac veins.

4. Thrombosis of iliac veins and vena cava (date not clear, possibly at the onset of the mental symptoms, possibly fifteen days later) and its sequelæ.

5. Acute delirium, difficult logically either to connect with or to disconnect from the thrombosis and bacteriemia discovered at autopsy.

6. Death from septicemia and pulmonary thrombosis.

The case detailed above raises the question whether the incidence of bacteria of low toxicity can determine insanity of the type of acute delirium. Many textbooks seem to admit something of the sort in their groups of *infectious deliria.*[7] It must be conceded, however, that the precise relationship of infection to delirium in its psychiatric sense is still far from clear.

As to the toxic value of staphylococcus albus, writers are not wholly clear. Genuine cases of albus septicemia are not unknown. The remarkable work of Winslow on the Coccaceæ[8] has served to unify rather than separate the staphylococci of various sorts. Kraus and Pribram[9]

(1906) have shown that many varieties of staphylococci produce a true toxin which will pass into the culture filtrate and produce an antitoxin; the toxin in question appears to poison the heart especially. Panichi[10] (1906) was able to cultivate the albus repeatedly over weeks and months from the blood of two subjects who otherwise gave no noteworthy signs of infection. Similar results with other organisms, especially in convalescence, are serving to overthrow our older notions of the essential injuriousness of bacteriemia. Such bacteriemia of unknown atrium may readily permit infection and thrombosis of tissues under such conditions as those of the iliac veins in the case above described. Moreover, it does not overstep the bounds of probability to state that a variety of symptoms, among them mental, may accrue from such low-grade infections.

The hypothesis that drug-like products of bacteria, or bacteria themselves drug-like in action, may produce mental symptoms, is certainly far from unlikely, though it is also true that idiosyncrasy or special sensitization may be essential to permit the development of such symptoms.

It is obvious, however, that psychiatric clinics are not working this field intensively, and for such work we wish to put in a plea. Routine blood cultures and carefully chosen immunity tests (especially those just recently developed for other purposes as a result of the work of Bordet and others[11]) in such cases would go far to clear up these obscure relations. Perhaps only by such intensive work can the mechanism of certain types of insanity be learned.

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XXV

A STUDY OF THE DEMENTIA PRÆCOX GROUP IN THE LIGHT OF CERTAIN CASES SHOWING ANOMALIES OR SCLEROSES IN PARTICULAR BRAIN-REGIONS.*

By E. E. SOUTHARD, M. D.

CONTENTS.

I. The Schism over Dementia Præcox 121
- Intoxication or dissociation.
- Apparent hopelessness of cortical cytopathology.
- Satellitosis of the deeper cortex layers (Alzheimer).
- French confirmation.
- Sioli's findings.
- Alzheimer's proof that dementia præcox is an organic psychosis.
- Differentiation possible between katatonic and maniacal excitement.
- Similar disintegration products in the brains of katatonia and of toxic delirium or severe visceral disease.
- *Hirntod.*
- Terminal infections in the insane remarkably common (Danvers data).
- Acute cytopathological changes must remain hard to interpret.
- Stratigraphic alterations (deep-layer satellitosis) important, but also not differential.
- The topographic idea in the anatomical investigation of dementia præcox.

II. Material, with Statistical Analysis 127
- Sixty-three cases of probable or possible dementia præcox.
- Classified by age at death.
  - by age at onset.
  - by duration of symptoms.
- Superficial analysis into forms.
- Brain weights by sex.
  - by age at death.
  - by clinical forms.
  - by duration of disease.
- Heart, liver, spleen, and kidney weights.
- Summary.

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III. Gross Anatomical Analysis of the Brain Findings........... 132
Object of the analysis.
Exclusion from prior consideration of cases of coarse cerebral atrophy.
Exclusion of cases showing focal destructive arteriosclerotic lesions.
Exclusion of cases of chronic diffuse leptomeningitis.
Dural and calvarial conditions.
Nineteen out of thirty-seven cases show macroscopic lesions.
Pre-Rolandic group.
Post-Rolandic group.
Infra-Sylvian group.
Cerebellar group.
Other macroscopic cases.
General grouping: 1, complicated cases (excluded from prior consideration (40 per cent); 2, cases with minor macroscopic lesions (31 per cent); 3, cases without observed macroscopic lesions (29 per cent).
Clinical analysis of thirty-seven chosen cases, with elimination of eight.
Fifty-two per cent of non-complicated chosen series show macroscopic lesions.
Incidence of tuberculosis in this series.
of other somatic complications.
Summary.
IV. Clinical and Anatomical Analysis of Fifteen Cases of Dementia Præcox Selected as Showing Certain Minor Gross Lesions of the Nervous System.................. 138
Correlations.
Condensed histories and autopsy protocols in fifteen cases.
The question of congenital anomalies *vs.* acquired lesions.
Summarized impressions of each case.
Acquired lesions probable in fourteen, congenital in eight, of fifteen cases.
Anatomo-clinical correlations.
Pre-Rolandic group, with frontal-paranoid correlation.
Post-Rolandic group.
(a) post-central—superior parietal—katatonic correlation.
(b) occipital subgroup.
Infra-sylvian group.
Cerebellar group, katatonic.
Provisional grouping of fourteen cases without recorded gross lesions.
Four cases in which gross lesions *should* probably have been recorded.
Probable actual proportion of gross lesions in our series 68 per cent.

Necessity of intensive inspection *and palpation* of brains at autopsy.
Probable actual proportion of gross and microscopic lesions in our series 86 per cent.
V. The Topographic Idea in the Study of Dementia Præcox and Allied Conditions 168
Brain "changes" in functional psychoses.
Is insanity brain-disease?
If insanities are brain-diseases, the brain-*parts* involved should be specified.
Wernicke's generalization.
The diabetes mellitus analogy—mental symptoms not necessarily cerebral, as glycosuria not renal in origin.
Universal cytopathological changes not likely in dementia præcox.
Analogy of dementia præcox and general paresis.
Random blocks of brain tissue, showing satellitosis, infrastellate gliosis, or disintegration products, not likely to solve problem of pathogenesis of symptoms.
VI. Conclusions 172

I. The Schism over Dementia Præcox.

When it became apparent that the psychiatric world must needs split over the genesis of dementia præcox, one party describing it as a species of intoxication with brain damage and the other as a dissociative mental disease without structural damage to the brain, one found one's mind almost wholly open in the matter. Perhaps, at the outset, one was not quite ready to admit dementia præcox (Kraepelin's disease) among such relatively immortal entities as general paresis and hysteria, for example. The dissociation hypothesis possibly seemed the wider of the two, permitting each case to be a law unto itself in such wise that a proper diagnosis reasoned into a fairly full katamnesis.

In any event it was gratuitous to hypothecate a toxine *toto coelo* and much more innocent to assume dissociations, especially if one could give precise descriptions of these for a number of typical cases. To be sure, some workers asserted characteristic satellitoses and other evidence of neuronic disease in the lower cortex-layers of the cerebrum; but these findings were perhaps inconstant, probably shared by other types of disease, possibly secondary either to the disease or to something else, and certainly incapable of affording any explanation of the mechanism of dementia præcox.

If one scanned the situation in neuropathology, the outlook was not bright. Restricting oneself to the cerebral cortex alone, cytopathology appeared to have fallen on evil days. Nissl had given up his specific nerve-cell intoxication pictures. Alzheimer's methods for split products of nerve-cell metabolism had not been developed or fully applied. And, in any case, the effects of terminal complicating disease (intestinal, pulmonary, bladder, and the like) with a variety of intercurrent infections and intoxicatons seemed to render dubious the outcome of almost any strictly cytopathological study, at least such as would contemplate symptomatic correlations. To conceive a "katatonic storm" sweeping through the cortex and leaving behind it a characteristic trail was within reason, but surely difficult of proof in the midst of so many cortical storms about the point of death.

Stratigraphic considerations were more hopeful. In fact, ever since Alzheimer's brief paragraph in 1897—*Ebenso findet sich ganz zweifellos bei der Katatonic eine pathologische Gliafaserbildung in der Rinde, anscheinend auf gewisse Rindenschichten* (*und die Markleiste*) *beschränkt*[1]—there has been an ever recurrent assertion that satellitosis and correspondent nerve-cell disorder of the inner cortex-layers are characteristic of dementia præcox, or at least of its katatonic form. In fact these findings were supposed to draw together the two diseases, dementia præcox and general paresis, since both showed the same changes, complicated in the latter by a multitude of other stratigraphic changes as well as by exudation.

Such opinions are not confined to Germany. Thus, in France, Klippel and Lhermitte, 1908,[2] consider dementia præcox to be due to a progressive atrophy of the association neurones. The lesions of dementia præcox, they say, are all essentially neuroepithelial, *i. e.*, confined to nerve-cells and neuroglia, and never essentially vasculoconjunctive, or, as we should expressly ectodermal, never mesodermal. The fundamental lesion is "a progressive atrophy of the nerve-cells of the deep cortical layers and disappearance of the interconnecting processes," with neuroglia proliferation running *pari passu* with the atrophic process. Meningovascular lesions, miliary hemorrhages, congenital malformations, terminal lesions due to cachexia or infection, are frequent, but are not indispensably found. Even cerebellar atrophy, and various instances of visceral hypoplasia, are simply signs of frail organisms, which either precede without causing dementia præcox or are purely incidental effects thereof. Klippel, in discussion, admitted that similar neuroepitheliæ (ectodermal) lesions were found in other chronic mental diseases.

Perhaps no work has been more widely quoted in this direction than that of Sioli, done partly at Munich under Alzheimer and partly at Bonn and summarily reported in 1909. Sioli's statements refer, however, only in part to stratigraphic considerations.

Sioli in his brief *Autoreferat*, 1909,[3] states that he found *in all parts examined* of 20 cases of dementia præcox certain evidences of destruction of nerve tissue. A portion of Sioli's data is cytopathological (nerve-cell disease with increase of Scharlach-stainable lipoids), but he indicates that the process may lead to atrophy or disappearance of cells, amounting in places to distinct stratigraphic disorder. Degenerative products were found accumulated in clear non-cellular spaces about the vessels, and protagonoid and Scharlach-stainable substances were found in tissues and in adventitial cells *en route* to the vessels. Inflammatory exudation was quite lacking. Perivascular and periganglionic glia-cell proliferation, fibrillary gliosis in the subpial zone, in deep cortex-layers, and in the white matter, alterations of glia-cell cytoplasm, amœboid neuroglia in the white matter occurred. The severest cases, especially those with their perivascular spaces packed with degeneration products, are thought to correspond with acute katatonic exacerbations.

Alzheimer, in his masterly statement concerning split products of nerve-cell and fibre metabolism, 1910,[4] maintains that much new light has been thrown, by his new methods and adaptations of old ones, upon such conditions as status epilepticus, severe paralytic attacks, deliria, and katatonic excitements, and he believes that anyone using these methods will be convinced that dementia præcox and epilepsy are severe organic diseases. Alzheimer would almost risk differentiating histologically between a katatonic excitement and a mania, because the katatonic case will show characteristic amœboid glia-cells, whereas the mania will not. For the purpose of this differentiation, severe disease of the other viscera must not step in to complicate the picture since such disease may bring out the amœboid glia-cells in the nervous system. Again, a severe toxic delirium at its height and a severe katatonic excitement at its height will exhibit similar changes (just as the posterior columns of a tabes and a spinal transsection might be confused under certain circumstances from the granule-cell content of both). The fact seems to be that "organic" changes can now be demonstrated in a number of conditions formerly termed "functional." The differentiation of katatonia remains difficult, however, on account of precisely the conditions mentioned by Alzheimer, toxic delirium and severe bodily disease, which may produce somewhat the same pictures.

One remarkable case of sudden death in a stuporous katatonic who had no demonstrable physical disease is mentioned by Alzheimer to show that, without loss of any nerve-cell or degeneration of a single axis-cylinder, a true *Hirntod* may occur due to changes demonstrable by methods for the split products.

Unfortunately for the neuropathologist, such cases of pure *Hirntod* are rare. In the Danvers State Hospital material, infection at the time of death is almost the rule. Exact experiences with the cultivation of the more easily growing organisms from the blood and cerebrospinal fluid in 150 unselected cases have been communicated by Gay, Canavan, and myself.[5][6] Cerebrospinal fluids are particularly prone at death to show organisms. This experience, as well as an inspection of the great members of tuberculous and acute infections in our material, caused us to discount in advance the cytopathological change *per se* and to hold somewhat in doubt the acute or recent neuroglia change as indicating mental disease. The asserted stratigraphical changes (cell-atrophies and losses in lower cortex-layers and correspondent satellitosis) seemed more trustworthy, but obviously less differential (seen also in general paresis and in some senile cases).

The status of the dementia præcox question may be summed up as follows:

One body of workers prefers to describe dementia præcox in such terms as *dementia sejunctiva* (Gross[7]), *Missverhältniss zwischen Affekt und Vorstellung* (Kölpin[8]), *dysphrenia* (Wolff[9]), *dementia dissecans* (Zweig[10]), *schizophrenia* (*Zerreissung oder Spaltung der psychischen Funktionen*) (Bleuler[11]), *Apraxia ideatrix* (Dromard[12]), emphasizing in general the dissociative factors which emerge upon psychological analysis of the more clearly cut cases. "Disruptions of judgment," "specific factors in individual cases," "unpsychological reactions," "intrapsychic ataxia" or more specifically "noothymopsychic ataxia," "intrapsychic inhibition," "psychogenic conflicts," "psychological dispositions," "psychic causos," "psychic trauma," are phrases picked almost at random from certain modern discussions.[13 14 16]

Other workers pin their faith to the supposed "organic" character of this disease. The ground of this belief is often scarcely more than that the disease is essentially deteriorative on the mental side and hence *must* be "organic" on the cerebral side. Others set much store by autointoxication and believe that the effects of autointoxication must be registered in the cerebral cortex, could we but read it aright. Proceeding from the dictum that insanity and, therefore, dementia præcox are brain diseases, these workers argue that dementia præcox is presumably a destructive disease of the cerebral cortex, after the manner of general paresis.

A few workers accord significance to both the functional psychic features and the organic cortical features. There is, however, a general tendency to take sides, with the almost universal feeling that the histologists have not satisfactorily proved the "organic" nature of the disease.

I was instigated to the analysis of my own material by the conviction that, though the histopathologists had not proved their point beyond peradventure, the functionalists were in the same plight. I had been engaged upon an analysis of cases of mental disease with onset after the fiftieth year,[16 17] and had there come upon so many instances of satellitosis in the deeper layers of the cortex without distinct katatonic features clinically that I had been disposed to discount the differential character of deep-layer gliosis for any type of mental disease. This reaction, in brief, appeared to be a necessary and natural result of destructive processes involving these layers, and the deposition or increase of neuroglia cells in this locus did not assume to my mind the differential character of such findings, as, *e. g.*, the plasma cell exudate of general paresis. Even the plasma cell, as all will admit, is not *sensu strictiori* pathognomonic for general paresis (witness trypanosomiasis, not to mention tuberculous and frankly luetic processes). Gliosis of the deep layers of the cortex is obviously far less differential than plasma cell exudation, if only because normally we find neuroglia and satellite cells in this region.

Feeling a deal of uncertainty about the differential value of stratigraphic alterations and especially of satellitosis, I was also not disposed to believe that dementia præcox would turn out to be a diffuse cell disease. All that Alzheimer maintains, if I understand him aright, is that anyone who chooses to examine dementia præcox material by certain methods can convince himself that it is invariably an " organic " disease.[18] It would be a much longer step to assert that the changes invariably found are differential changes. Indeed, deliria and severe physical disease are consistent with the same changes.

Neither stratigraphic changes nor cytopathological changes, taken as exhibited *throughout a brain,* appealed to me as likely to throw much light on the immediate mechanism of dementia præcox. Indeed these changes bring up more new problems than they solve old ones in the wide field of neurobiology.

The *topographic idea* then occurred to me. In making, some years ago, an analysis of the first 1250 autopsies of the Danvers State Hospital and collecting the lesions of different parts of the brain in card-catalogue form, I had been much struck with the preponderance of brain lesions in certain areas. The frontal incidence was particularly high, and this, I took to be due to the greater liability of the frontal tissues (on the stock evolutionary grounds). Having no convenient opportunity to correlate these findings with clinical data (a want now happily supplied by the index of clinical symptoms which Dr. Page has had constructed), I did not further work up these relations.

In connection, however, with work on encephalitis,[19] on gliosis,[20] [21] and especially on the " soft brain," [22] I had begun to gather unusually careful data concerning focal and general variations in consistence of brains. I had, therefore, some hope that my series would prove unusually suitable for topographic study.

Upon analysis, as the sequel will prove, not merely focal scleroses, but also easily identifiable macroscopic atrophies (or aplasias) were found in a surprisingly large number of cases. My topographic data depend, therefore, only in part upon the palpable mild scleroses which I had been especially studying.

On the basis of the anatomical data and without necessarily any reference to microscopic studies (which have been carried out more or less thoroughly in the series), I wish to commend the topographic idea concerning lesions in dementia præcox to neuropathologists. Whether a superior frontal atrophy or a postcentral aplasia is or is not superior to a psychic scar or ataxia, as really explanatory of the mechanism of dementia præcox, I will not pretend to say. In any event, the brains of all dementia præcox cases should be carefully examined.

II. Material, with Statistical Analysis.

The autopsy material of the Danvers State Hospital Laboratory from May, 1902, to January, 1910 (including the services of Drs. A. M. Barrett, E. E. Southard, and a portion of Dr. H. M. Adler's), consists of 647 cases. Sixty-three of these have been chosen, on clinical grounds, as probable or possible examples of dementia præcox. The 10 per cent thus chosen constitute the maximum rather than the minimum number of possible cases, since it was thought best to include certain doubtful cases for purposes of comparison. As will presently appear, several of the cases are so clouded by other factors, such as certain congenital features, alcoholism, or attacks suggestive of manic-depressive insanity, that the diagnosis of dementia præcox may appear extremely doubtful. It was felt that histological features might serve to extract the true cases.

As it is extremely desirable not to confuse phenomena of a normally aging brain with possible findings based on mental disease, the age of the subjects at death is important. The series is quite representative.

TABLE I.

Classified by decades according to age at death, the material shows:

11	cases	dying	in the	third	decade	(21-30)=	8 male,	3 female
19	"	"	" "	fourth	"	(31-40)=	7 "	12 "
12	"	"	" "	fifth	"	(41-50)=	3 "	9 "
11	"	"	" "	sixth	"	(51-60)=	6 "	5 "
8	"	"	" "	seventh	"	(61-70)=	7 "	1 "
2	"	"	" "	eighth	"	(71-80)=	2 "	0 "
—							—	—
63						(21-80)=	33 "	30 "

It is also necessary to secure a representative series from the standpoint of age at onset. The series even includes two cases with strongly congenital coloring.

TABLE II.

Classified by decades according to age at onset, the material shows:

2	cases with congenital features (possibly imbecile)			= 2 male,	0 female
6	" " onset in the second	decade	(11-20)	= 6 "	0 "
28	" " " " "	third "	(21-30)	= 13 "	15 "
20	" " " " "	fourth "	(31-40)	= 9 "	11 "
7	" " " " "	fifth "	(41-50)	= 3 "	4 "
—				—	—
63				33 "	30 "

It is essential to know how long the morbid process may be supposed to have lasted. Although many of these cases are not at all progressive, yet in many others slow transitions in clinical disease-type are exhibited. The total durations are given in

TABLE III.

Classified by duration of symptoms in hemidecade periods, the material shows:

18	cases under		5	years in duration........	8 male,	10 female
11	" between	6 and	10	years in duration,	5 "	6 "
10	" "	11 "	15	" " "	3 "	7 "
3	" "	16 "	20	" " "	2 "	1 "
7	" "	21 "	25	" " "	4 "	3 "
4	" "	26 "	30	" " "	2 "	2 "
3	" "	31 "	35	" " "	3 "	0 "
3	" "	36 "	40	" " "	2 "	1 "
1	" "	41 "	45	" " "	1 "	0 "
2	" "	46 "	50	" " "	2 "	0 "
1	" "	61 "	65	" " "	1 "	0 "
—					—	—
63					33	30

Although it is well known that various clinical phenomena are rather thoroughly commingled in this disease, making the older distinctions hard to maintain and more or less justifying Kraepelin in his union of types under a single caption, yet certain features do particularly characterize some cases, and the following table presents the impressions which these cases made, so to say, in the rough, before intensive analysis.

TABLE IV.

Superficial Analysis of Cases.

Hebephrenic	5	cases,	2	male,	3	female
Katatonic	17	"	9	"	8	"
Paranoid	30	"	18	"	12	"
Dementia-præcox-like:						
Imbecile	1	"	1	"	0	"
Alcoholic	1	"	1	"	0	"
Manic-depressive, involutional and unclassified	9	"	3	"	6	"
	63	"	34	"	29	"

There was such an admixture of symptoms in several of the cases, or symptoms of doubtful import, that possibly the katatonic cases should number 20, and the paranoid cases, 32. Imbecile traits came in question in seven cases in all, though possibly not to obscure the eventual diagnosis in more than three. Alcoholism can, with difficulty, be disengaged from the clinical picture of five cases. The at times doubtful, or eventually unclassified cases, which have been chosen to study with this group, number 15; but of these perhaps eight only can be fairly claimed as not instances of dementia præcox; and, if a somewhat liberal definition be admitted, all these cases will warrant consideration. As Table IV indicates 52 cases (29 male, 23 female) probably belong in the group with some certainty on clinical grounds.

In the process of anatomical analysis, much may be gained from the weight correlations of certain organs. If the brain weights stand up well, we at least have indication that no such conditions as those underlying general paresis or cerebral atrophy are present. The brain weights in this series correspond well with the normal, though they show a slight tendency to reduction (2 per cent).

TABLE V.

Brain Weights by Sex.

Male (26 cases)	1336	dementia	præcox,	1357	normal	(Vierordt)
Female (29 cases)	1218	"	"	1235	"	"
Differences	118	"	"	122	"	"
Percentages:						
Male	98%	"	"	100%	"	"
Female	98%	"	"	100%	"	"

An analysis of the brain weights according to age at death yields by no means so even a curve, doubtless because the numbers are too small for this particular purpose. The results are as follows:

TABLE VI.

Brain Weights by Decades in which Death Occurred.

Male	21-30,	6 cases	1333	dementia	præcox,	1358	normal	(Boyd)
Female	21-30,	3 "	1278	"	"	1239	"	"
Male	31-40,	5 "	1476	"	"	1366	"	"
Female	31-40,	11 "	1194	"	"	1222	"	"
Male	41-50,	3 "	1350	"	"	1348	"	"
Female	41-50,	9 "	1237	"	"	1214	"	"
Male	51-60,	6 "	1353	"	"	1345	"	"
Female	51-60,	5 "	1222	"	"	1225	"	"
Male	61-70,	5 "	1364	"	"	1315	"	"
Female	61-70,	1 "	1100	"	"	1210	"	"
Male	71-80,	1 "	1390	"	"	1290	"	"

It might be suspected that the different forms of dementia præcox would lead to different degrees of brain-weight reduction. The weights in the hebephrenic, katatonic, and paranoid cases, in accordance with the clinical analysis of Table IV, have been arranged:

TABLE VII.

Hebephrenic,	male	2 cases	1338	1357	normal	(Vierordt)
	female	3 "	1168	1235	"	"
Katatonic,	male	9 "	1329	1357	"	"
	female	8 "	1193	1235	"	"
Paranoid,	male	12 "	1309	1357	"	"
	female	11 "	1240	1235	"	"

The differences are all less than 70 grams, and the weights are consequently within five per cent of the assigned normals.

Since the duration of the disease, though it certainly does not vary with the duration of any active process in all cases, might be supposed to bear some relation with the extent of any destructive process, the weights have been arranged according to duration:

TABLE VIII.

Cases with duration under 10 years:					
Male		1331	1357	normal	(Vierordt)
Female	16 cases	1223	1235	"	"
Cases with duration 11-20 years:					
Male	5 cases	1261	1357	"	"
Female	7 "	1243	1235	"	"
Cases with duration over 20 years:					
Male	10 cases	1375	1357	"	"
Female	6 "	1173	1235	"	"

Obviously these figures produce no even curve; but, should they be confirmed by other material, the interference could certainly be drawn that these brains stand wear and tear particularly well.

If such figures tend to show that no coarse katabolic effects evince themselves in the brains of this group, it is interesting to inquire whether any evidence of such disorder can be traced in other organs by this method.

TABLE IX.

Heart Weights.

Male 31 cases	281	
minus 3 hypertrophies (500 + g.)	244	313 normal (Vierordt)
Female 27 cases	264	
minus 1 hypertrophy	253	310 " "

TABLE X.

Liver Weights.

Male 30 cases	1369	1579 normal (Vierordt)
Female 28 "	1257	1526 " "

TABLE XI.

Spleen Weights.

Male 30 cases	160	
minus 1 case wt. 870	132	149 normal (Vierordt)
Female 27 cases	106	180 " "

TABLE XII.

Combined Kidney Weights.

Male 31 cases	280	277 normal (Vierordt)
Female 29 "	255	264 " "

Tables IX to XII appear to show that certain organs of the trunk are more disposed to evince losses in weight than is the brain in dementia præcox. The kidney weights, however, stand up well. The weight of the spleen, as always, showed marked variations, and these variations largely depend probably on certain terminal conditions independent of mental disease.

Reductions in average weights of heart and liver reach a little over eight per cent, for both males and females in both series. It is hard to draw a significant conclusion therefrom.

To sum up the data of this section, we learn from a fairly representative series of cases of dementia præcox and similar diseases that a reduction in brain weight of two per cent is perhaps to be expected in the total group, that the reductions in brain weight of five per cent occur in certain forms (here a larger number of cases is required for deductions), that the brain weights do not undergo progressive reduction with the duration of the disease, and that the hearts and livers of the series show in general a reduction of eight per cent in weight. Since the weights of the trunk viscera probably vary rather uncontrollably in the present state of knowledge (the factors of muscular activity and of nutrition in these patients come particularly in question), it is plain that more stress must be laid on brain conditions. The brains must be approached, therefore, with the premonition that changes, if any, will be fine changes, and possibly qualitative and transformatory rather than destructive.

III. Gross Anatomical Analysis of the Brain Findings.

As it is our object to show *either,* first, that there are no characteristic brain findings in this series of cases *or,* secondly, that there are characteristic findings common to the series, it is obviously necessary to exclude cases with certain features which we are sure are not characteristically allied with dementia præcox. Such complicating features are *coarse cerebral atrophy* and *regionary arteriosclerosis.* These features complicate and sometimes influence the course of dementia præcox; but it is certain that arteriosclerosis and highly probable that coarse cerebral atrophy are not characteristically associated with the disease.

As is well known, the question, whether brain atrophy exists, cannot be safely answered from the brain weight alone, since apparently high weights are consistent with atrophy of originally large brains, and apparently low weights may mean simply that the original weights were low. Qualitative data are safer guides here.

Five brains gave the qualitative impression of *generalized atrophy.* All these cases were of long total duration (11 years or more).

TABLE XIII.

Autopsy Number.	Clinical Number.	Sex.	Age.	Disease-Type.	Duration.	Terminal Disease.	Brain Weight.
752.	9888.	F.	64.	hebephrenic,	9y.	pneumonia, 7d.	1100.
958.	10738.	F.	37.	paranoid,	11y.	exhaustion, 1m.	1210.
1266.	7559.	F.	58.	paranoid,	13 ++ y.	dysentery, some weeks.	1250.
1274.	11027.	M.	56.	katatonic,	31y.	hemiplegia, 1m.	1365.
1297.	7511.	F.	47.	paranoid,	19y.	cancer of uterus, 2 + m.	1390.

It seems safe to eliminate this group from prior consideration, despite the fact that the gliosis shown may be more or less closely related with dementia præcox.

One of the best indices of damaging local arteriosclerosis is afforded by *cysts of softening,* which were found in three cases, 1274 and 1297 of Table XIII, and 1171 (5986, F., 43, paranoid, 17+(30?) y., brain weight 1115g.), also excluded from prior consideration.

Also it may be safer at first to exclude seven cases (1099, 13180, M., 67; 1121, 13398, F., 56; 1174, 9769, F., 48; 1258, 2, M., 64; 1270, 617, M., 68; 1337, 15017, F., 45; and 1368, 12120, M., 56) on the score of *marked sclerosis of vessels of the circle of Willis.* It is certain that this sclerosis has no direct effect upon the mental life; but there is at least a suspicion of vascular disease in the finer branches in such cases (only two of which in this series, viz., 1337 and 1174, are under 56 years of age).

It is noteworthy that we are required to exclude on these grounds (grounds, namely, of complicating "organic" brain-disease) only about 20 per cent of our series. This confirms the impression gained from our statistical analysis of the brain weights.

There is another general condition, frequently found in cases of all descriptions (both sane and insane), which might be considered to have some bearing especially upon the histology of the superficial layers—*chronic leptomeningitis of diffuse distribution* (to the focal distributions we shall return in a moment). Eleven cases (842, 904, 913, 943, 958, 1014, 1025, 1027, 1093, 1234, 1338) may be excluded on this ground. These 11 and four others (already excluded) yield another perhaps surprisingly small percentage (about 22 per cent) of cases showing diffuse chronic leptomeningitis.

For completeness are also presented the data concerning

TABLE XIV.

Dural and Calvarial Conditions.

Arachnoidal villi unusually developed	3 cases
Thickening of dura mater (not included under adhesions)	4 "
Chronic internal hemorrhagic pachymeningitis	3 "
Dense calvarium	9 "
Thick calvarium	6 "
Thick and dense calvarium	2 "
Thin calvarium	3 "
Calvarial adhesions of the dura mater	25 "

If we rely upon the statistical analysis of Section II, we cannot be so sure that mild *focal lesions of an atrophic or sclerotic nature* have nothing to do with processes in dementia præcox, since these lesions will not appreciably influence brain weights. It is, of course, *à priori* unlikely that such circumscribed foci, which are doubtless in the vast majority of instances due to some degree of local tissue destruction, can correspond with the extended series of vital reactions which we term dementia præcox. Nevertheless, it is wise to examine our series carefully for foci of a slightly destructive or perhaps purely irritative character which might bear on the course of certain cases.

Consequently, excluding as diffusely atrophic five cases, as markedly arteriosclerotic (cysts of softening or basal cerebral arteriosclerosis) eight cases, as showing diffuse chronic pial changes 11 cases, we remain with a material of 39 cases, which deserve primary consideration from the standpoint of *possibly significant focal brain lesions.* Obviously the results of the search in these 39 cases (two of which must be excluded through inadequate protocols) may be applied, with due caution, to the remainder.

A group of 14 cases amongst these 37 "non-organic" cases showed certain *minor lesions* made out in the gross, but *not frankly destructive, some possibly congenital in origin.* A summary view of these cases is presented in

TABLE XV.

MINOR MACROSCOPIC BRAIN LESIONS IN DEMENTIA PRÆCOX.

I. Pre-Rolandic Lesions.

Autopsy Number.	Clinical Number.	Sex.	Age.	Disease-Type.	Duration.	Frontal Lobe Lesions.
840.	11211.	F.	38.	katatonic,	3y.	Atrophy and gliosis of frontal lobes.
1062.	7987.	F.	38.	paranoid (alcoholic)	11 + y.	Gliosis of superior frontal, prefrontal, and orbital gyri.
1143.	8823.	F.	47.	paranoid or katatonic,	10y.	Gliosis of frontal, including orbital, gyri (v. also cerebellum).
1294.	10862.	F.	37.	paranoid,	6y.	Frontal lobe gliosis (v. also post-Rolandic and cerebellar groups).
1310.	13582.	F.	28.	hebephrenic mannerisms,	4y.	Frontal lobe gliosis (v. postcentral group).
1358.	10580.	M.	24.	katatonic,	10y.	Gliosis of left inferior frontal lobe.
1360.	10168.	M.	51.	suicidal,	10y.	Atrophy of prefrontal gyri.

II. Post-Rolandic Lesions.

Occipital Region Gliosis.

1137.	6531.	M.	35.	paranoid, later katatonic,	15y.	Right superior parietal microgyria (atrophia?).
1168.	11863.	F.	24.	hebephrenic paranoid?,	3½y.	Bilateral aplasia of postcentral gyri.
1298.	14591.	F.	36.	katatonic,	10m	Right postcentral atrophy (v. discussion).
1310				See Frontal Group		Left postcentral aplasia or atrophy.
1149.	11641.	M.	57.	paranoid,	32y.	Occipital region gliosis.
1294				See Frontal Group		Occipital region gliosis.
1317.	12143.	F.	44.	paranoid,	21y.	Occipital microgyria.

III. Infra-Sylvian Group.

Cerebellar Lesions.

1319.	14597.	F.	31.	paranoid, (imbecile)	8y.	Superior temporal anomaly.

IV. Cerebellar Lesions.

1034.	12756.	M.	35.	first paranoid later katatonic,	2y.	Sclerosis of dentate nuclei of cerebellum.
1143				See Frontal Group		Sclerosis of right dentate nucleus, culmena, and clivi of cerebellum. Pons and olives firm.
1168				See Post-Rolandic Group		Sclerosis of right dentate nucleus, cacumena, and clivi of cerebellum. Sclerosis of olives.

A somewhat similar small group of four cases has shown certain appearances in the spinal cord, indicating abnormality of quite doubtful interpretation.

TABLE XVI.

Gross Lesions of the Spinal Cord.

Autopsy Number.	Clinical Number.	Sex.	Age.	Disease-Type.	Duration.	Gross Lesions of the Spinal Cord.
1317				See Post-Rolandic Group		Cervical portion abnormally firm.
1319				See Infra-Sylvian Group		Cervical cord abnormally large.
1335				See Table XVII		Cord abnormally small.
1350.	4820.	M.	62.	katatonic,	35 + y.	Gliosis of lumbar spinal cord.

Here then, as indicated in Tables XV and XVI, is a group of 15 cases showing certain minor chronic lesions (or evidences of aplasia) in the central nervous system of quite doubtful, though certainly very varied, origin. Adding four more cases of *generalized cerebral sclerosis* of a mild form, not associated with gross atrophy, viz.

TABLE XVII.

Autopsy Number.	Clinical Nnmber.	Sex.	Age.	Disease-Type.	Duration.	
991.	11047.	M.	35.	paranoid,	11y.	Brain weight 1170 grams.
1135.	11296.	F.	28.	katatonic,	6y.	Brain weight 1430 grams.
1303.	11624.	F.	55.	hebephrenic,	25y.	Brain weight 1220 grams.
1335.	13648.	M.	32.	katatonic (alcoholic)	20y.	Brain weight 985 grams.

we obtain a total of *19 cases of slightly, though macroscopically, abnormal central nervous system in a series of 37 cases, selected as not showing coarse complicating features like brain atrophy, intracranial arteriosclerosis, cysts of softening, and the like.*

These 19 cases, or at all events a certain number of them, demand attention as a group of dementia præcox cases with lesions of doubtful interpretation, but not readily set aside as non-significant.

If we should group our cases up to this point, we should obtain (1) *complicated cases,* showing gross lesions certainly not related with dementia præcox, 40 per cent, (2) *cases with minor lesions* having a doubtful relation to dementia præcox, 31 per cent, and (3) a residuum of *cases without observed gross lesions,* 29 per cent.

It will be wise at this point to analyze the cases of groups (2) and (3), *i. e.,* the non-complicated cases from a clinical point of view. The 37 cases are distributed as follows:

TABLE XVIII.

Hebephrenic	4	2	male,	2	female
Katatonic	12	5	"	7	"
Paranoid	13	7	"	6	"
Alcoholic	1	1	"	0	"
Doubtful	7	3	"	4	"

If we eliminate the alcoholic (1240, no gross lesions) and doubtful cases (819, 939, 1151, no gross lesions; 1143, 1360, frontal lobe lesions; 1350, spinal cord lesion; 1135, generalized gliosis, Compare Tables XV-XVII) for the time being, we obtain 52 per cent of our group (now reduced to 29 cases) showing minor lesions.

A microscopic analysis of the 15 cases showing minor lesions may indicate what type of lesion to look for in those cases which failed to show gross lesions. Lesions of this sort should be demonstrable by any method which displays cells and nuclei well.

In case the lesions should prove non-stratigraphical, *i. e.*, not ideally demonstrable by complete cell-counting, the task will be more difficult. The qualitative intracellular or special extracellular properties which this latter search would entail will require material very seldom obtained, material free from terminal complications. Cases hitherto reported have suffered perhaps from such terminal disease. Tuberculosis is a special offender in this direction. Tuberculosis occurred in our series as follows:

TABLE XV.

Tuberculosis in 63 Cases of Dementia Præcox.

Active forms	21	cases
Healed and chronic forms	16	"
All forms	37	"

Tuberculosis in 39 Chosen Cases.

Active forms	16	cases
Healed and chronic forms	7	"
All forms	23	"

In both series there is 58 per cent of tuberculosis, counting all forms. One case in three of the whole series either died with or showed an active form of tuberculosis, whereas about two cases in five of our chosen "non-organic" series showed similar active tuberculosis.

Whereas it has never perhaps been convincingly shown that active tuberculosis outside the nervous system can produce important non-exudative lesions within the nervous system, it is probably a sound policy to exclude such cases from a list *sans reproche*, especially if intracellular conditions are to be studied. This process would leave us with *23 cases free from coarse destructive brain lesions and from active tuberculosis.*

Nine cases showing *decubitus,* 10 cases of soft brain" (only one of which occurred in the non-organic series), and three cases of *edema of brain substance* might also offer obstacles to finer cytological analysis. For this purpose a list of 21 cases is available; but clinical doubts and difficulties remove eight cases, leaving 13 cytologically appropriate cases (840, 884, 891, 944, 1006 (typhoid fever), 1034, 1081, 1298, 1303, 1317 (carcinomatosis), 1350, 1358, 1360).

To sum up, we have divided our cases upon anatomical grounds into three groups, (1) cases complicated by gross destructive brain lesions (40 per cent), (2) cases having certain minor anomalies or mildly destructive or irritative lesions (31 per cent), and (3) cases without observed gross lesions (29 per cent). After excluding cases unsuitable for analysis on various grounds, we obtained a group of 29 cases, 15 of which (52 per cent) showed the minor anomalies and mild lesions just mentioned. It will be the task of the next section to study these 15 cases intensively to see whether they evince any common features. Later studies may then apply these observations to the rest of the series, in which significant lesions may well occur hidden among complications.

IV. Clinical and Anatomical Analysis of Fifteen Cases of Dementia Præcox Selected as Showing Certain Minor Gross Lesions of the Nervous System.

At this point it seems pertinent to inquire whether, upon a closer analysis of the cases which show minor gross lesions or anomalies, any hint of correlation between these lesions and individual clinical phenomena can detected. It must be pointed out forthwith that no very close correlation can be hoped for, since we deal with far less constant phenomena than, *e g.*, those of epilepsy. The histories, presented below in as condensed form as deemed advisable to offer a sound basis for clinical diagnosis, obviously betray far greater variations in course and qualitatively more complex features than would a similar number of histories of epileptics. But clinical and anatomical correlations even in epilepsy are difficult, despite the firm establishment of the "uncinate" group on an anatomical basis. In view of the clinical variety of the dementia præcox group, or even of the group of cases characterized by katatonic symptoms, it is at the outset doubtful whether a "frontal lobe group," a "postcentral group," a "cerebellar group" can be firmly established for dementia præcox. Obviously such a grouping should be earnestly essayed.

The *condensed histories,* drawn from the records of numerous workers (among whom may be mentioned Drs. H. W. Mitchell, H. A. Cotton, H. M. Swift, and Charles Ricksher, who have been at the heads of the various services during the major part of the time covered by these reports) and the *summarized autopsy protocols* (for which the pathologists, bacteriologists and assistant physicians named below have been responsible) are here presented.

Case I.—S. M., D. S. H., No. 12211, Path. No. 840. Female, 37, single, school-teacher. Born in Cambridge, Mass., of Irish parentage. Was a case of dementia præcox, katatonic type, of three years duration.

Heredity.—Negative.

Previous History.—Patient taught school from 22-35. In August, 1901, after a period of over-work, the patient became depressed ("had lost her soul"); her mind dwelt on suicide. Patient remained unoccupied; two weeks after onset of depression was committed to McLean Hospital, where she showed languor, slow movements, little spontaneous talk, a general effect of emotional gloom and certain somatic delusions ("bowels gone"). A brief attack of excitement followed, with confusion and resistiveness. Short periods of excitement followed with later increasing inertia, and little spontaneous talk. Seven weeks after commitment she began to show increase of muscular tension and had to be tube-fed.

Patient was transferred to Danvers Hospital April 1, 1903, and then showed a flushed face, clammy skin, and considerable acne. Pulse slow and weak, respirations shallow.

The katatonic signs consisted of an evenly distributed increase of muscular tension. Patient lay constantly in bed, on one side, with arms loosely adducted, hands clenched, legs flexed, chin and knees drawn together, eye-lids tightly closed, a fixed facial expression, with lips protruded.

At first patient would take food from a cup, but tube-feeding was later constantly resorted to.

Patient would flinch slightly to pin pricks, but would not move limb even if pin was deeply thrust. Risus sardonicus appeared at times. Occasionally, the eye-lids were kept half closed, and the eye-balls rolled upward.

Within six weeks, a slight physical failure was noted. Patient would occasionally speak at night. Later, talking spells occasionally appeared, such as "Go away," "Stop that," "Oh, what shall I do? I can't read. Oh, a thousand times. It is nothing at all"; or again, "I shall have to stop in this bed forever. God Almighty in Heaven, here I am talking, and I have no head. I am as empty as space. There is nothing in this bed, and I have no head. I have fixed everything wrong. It is terrible. Look, I am talking without a head. It is impossible. Is it not? An empty bed.

I am a skeleton bitch. This is a frightful impossibility." Looking at her hands she said, "These are not hands. How can I do this talking without a head? God help me. It is all wrong. I simply imagine that I see them. There is nobody here, the bed is empty. I don't know what I am doing."

Emaciation became rapid late in 1903, and patient died after a period of continued fever.

Anatomical Diagnosis (A. M. Barrett).

Cause of Death.—Phthisis pulmonalis.

Chronic Conditions.—Poor musculature. Malnutrition. Bilateral chronic adhesive (apical and posterior) pleuritis. Tuberculous cavity of apex of left lung. Cavitation and disseminated tuberculosis of upper lobes of both lungs. Enlarged bronchial lymph nodes. Bronchitis. Chronic fibrous ("milk patch") pericarditis.

Recent Conditions.—(Possibly bronchitis and bronchial lymphnoditis). Fatty liver (microscopic evidence). Fatty kidney (microscopic evidence, slight).

Nervous System.—Brain weight 1090 grams. Generalized increase of consistence of brain. Slight visible atrophy of gyri of both frontal regions. Cerebral cortex unusually dark in color, but without puncta cruenta.

Case II.—P. F., D. S. H., No. 10147, Path. No. 991. Male, 35, married, carpenter. Born in Nova Scotia of Nova Scotian parents. Was a case of dementia præcox, paranoid type.

Heredity.—Negative.

Previous History.—Masturbation; sexual excess. At 21 years married; five children. At 31 years "nervousness," loss of confidence, somatopsychic delusions ("heart gone," "insides working"). In hospital quiet, apathetic, hypochondriacal. Discharged at 35 and next year recommitted. Diagnosis, hypochondriacal paranoia. The diagnosis was later changed to chronic melancholia. Emaciation and suspicion of phthisis at 38 years. Signs of phthisis upon recommitment at D. S. H., October 25, 1902. Extremities blue, teeth poor. At first refused food. Groaning and complaints of pain and abnormal sensations. Disorientation (lack of interest?) for time and place.

"I can't speak because it pulls down and pulls up, and is wound around me." At no time katatonic signs, except mutism (possibly paranoidal origin).

Anatomical Diagnosis (A. M. Barrett).

Cause of Death.—Phthisis pulmonalis.

Chronic Condition.—Malnutrition. Poor musculature. Chronic obliterative pleuritis, bilateral. Phthisis pulmonalis, with cavitation and fibrosis. Chronic persplenitis. Chronic interstitial nephritis. Exostosis on inner surface of frontal bone. Adherent dura.

Acute Condition.—Acute fibrinous pericarditis (organism of colon group).

Nervous System.—Brain weight 1360 grams. Slight generalized cerebral gliosis.

Case III.—R. O., D. S. H., Nos. 11871, 12756, Path. No. 1034. Male, 35, single, shoe-factory operative. Born in Italy. Was a case of dementia præcox, at first paranoid, later katatonic, of two years duration.

Facts concerning heredity unknown.

Previous History.—Emigrated from Italy at about 23. Shoe-factory operative of average capacity. Easily affected by alcohol (some beer and whiskey daily). In March, 1904, stated that anarchists and socialists wished to kill him; that he heard men talking and singing in the next room; thought that people were going to "do him," and ceased to work steadily. In the course of five or six weeks patient began to feel that his friends had turned against him, and when a man borrowed his mandolin and returned it minus one string, patient reasoned that he was being hypnotized. At that time, the diagnosis lay between dementia præcox and alcoholic insanity, the former preferred.

Patient was committed to Danvers Hospital April 27, 1904. Undersized, unusually hirsute. There was slight swaying in the Romberg position. The knee-jerks were exaggerated. Patient was reticent. At one time said, "There is going to be something this side and then on the other side," making signs with his fingers around his head. Once asked to play cards, snatched the cards from the table and refused to give them up. Dulness and inactivity increased, with a tendency to stupor, interspersed with brighter intervals. Nine months after admission, periods with marked echopraxia and some cerea flexibilitas, with diminished response to peripheral stimuli, set in. Patient became reluctant to eat.

Discharged February 2, 1905, to go to Italy. Patient was readmitted October 5, 1905, with mutism, cerea flexibilitas, slight resistiveness on being roused, fixed facial expression, staring eyes and pouting lips. Slight albuminuria was now demonstrated for the first time. Automatism shortly developed, with prompt obedience to commands, such as protrusion of the tongue for incision. Patient habitually sat for hours with hands spread over knees, staring at the floor. Saliva was held in mouth for hours. Symptoms of pulmonary gangrene set in and patient died a week later, January 23, 1906.

Anatomical Diagnosis (E. E. Southard).

Cause of Death.—Gangrene of right lung.

Chronic Conditions.—Emaciation. Unequal pupils. Irregularity of right pupils (iris narrow above). Slight mitral valvular sclerosis. Small heart (150 grams, but left ventricle 1.5 cm. thick), and small aorta (5 cm. in circumference).

Acute Conditions.—Gangrene of posterior portion of right upper lobe of lung (culture, streptococcus pyogenes and diphtheroid organisms), with acute fibrinous pleuritis, bronchial edema, and swelling of bronchial lymph nodes. Septicemia (determined on culture, streptococcus pyogenes and diphtheroid organisms). Unusual hirsuteness.

Nervous System.—Brain weight 1410 grams. Dentate nuclei abnormally firm and yellowish.

Case IV.—D. R., D. S. H., No. 7987, Path. No. 1062. Female, 38, married. Born in Nova Scotia of Irish parentage. Was a case of dementia præcox, paranoid type, of eleven years duration.

Facts of heredity unknown.

Previous History.—At the age of 28, about a month before commitment to D. S. H., patient had been depressed and suicidal, with delusions that she was being killed, had been partially buried, had seen spirits, had had two hearts and was immortal. It appeared that the patient had been lately deserted by her husband and much over-worked. She had had three children, one living.

Shortly after admission, August 31, 1895, she was given the diagnosis of primary delusional insanity. She showed râles in both apices and edema of ankles. Patient worked in the laundry. Was occasionally reticent, but at other times freely stated her delusions. Tooth-aches and neuralgic pains she attributed to external influences. Was at times abusive, noisy and obscene. At other times would show no evidence of mental disorder for several weeks. In the course of two or three years, physical inertia increased, delusions could be still elicited, with somewhat less coherent explanations. Sample of conversation: "I was referring if you thought I felt well and if it was for your purpose to ask these questions. I proved it whether I am worthy of my home. There are two police stations and if you are acquainted with medical things you will see the church about me." Active auditory hallucinations appeared at times. The tuberculosis probable at admission became definite 10 years later. Patient died after a terminal disease of about four months. This patient apparently never showed well-defined katatonic signs, unless occasional reticence with physicians and a single period of mutism can be so interpreted.

Anatomical Diagnosis (E. E. Southard).

Cause of Death.—Phthisis pulmonalis.

Chronic Conditions.—Poor musculature. Malnutrition. Poor teeth. Lineæ atrophicæ of abdominal skin. Chronic obliterative pleuritis (right), and extensive adhesions of left pleura. Extensive bilateral tuberculosis with cavitation of lungs and bronchitis. Enlargement and induration of bronchial lymph nodes (tuberculosis, microscopically). Aortic, common iliac, internal iliac (slight), renal (microscopic), and (slight) coronary arteriosclerosis. Fatty liver with (microscopically) slight portal cirrhosis. Genitalia atrophic. Thyroid small (aberrant thyroid above bifurcation of trachea, right anterior, 2 x 1.5 x 0.5 cm.). Marrow of right femur red.

Nervous System.—Brain weight 1260 grams. Gliosis of superior frontal, prefrontal and orbital gyri. Brain (except gliotic areas and occipital gyri) and spinal cord (especially lumbar) reduced in consistence. Cerebellar cortex darker than cerebral cortex.

Case V.—M. R., D. S. H., No. 6531, Path. No. 1137. Male, 35, single. Shoe-factory operative. Born in Lynn, Mass., of Irish parentage. Was a case of dementia præcox, at first paranoid, later at times katatonic, and finally demented; of about 15 years total duration.

Heredity of insanity denied. Father possibly alcoholic. A brother died of tuberculosis.

Previous History.—September 1, 1891, patient developed a delusion that persons in an electric light plant opposite his shop were putting currents on him. Insomnia, constipation, lack of appetite, pains in the head and confusion of mind followed, and patient was committed to D. S. H., October 2, 1891, with exaggerated knee-jerks and little or no physical disorder. Apparent dementia increased. Unusual motions and gestures could not be explained by patient. At first he worked well in the brush shop, but later ceased work, became mute, and sat still in one place, smiling. The attendant could get patient to walk up and down the ward. Limbs were habitually blue and cold. In taking exercise, a certain number of steps were always taken and a certain crack in the floor was followed. When seated, the limbs were held fixed and the mouth open. At times the patient would sit gesticulating for long periods at a time. Later, the gestures and peculiar attitudes ceased, but mutism persisted. Once, in 1903, the patient whispered a few words. There was never any refusal of food during the Danvers stay. Death January 19, 1906.

Anatomical Diagnosis (E. E. Southard).

Cause of Death.—Phthisis pulmonalis.

Chronic Conditions.—Malnutrition. Chronic adhesive pleuritis of left upper lobe and right apex. Mitral valvular sclerosis. Brown atrophy of heart muscle. Small heart (170 grams, but left ventricle 1.3 cm. thick) and small aorta. Chronic interstitial nephritis. Dilatation of stomach. Right testis fibrotic.

Recent Conditions.—Tuberculous pneumonia of left lung, with acute fibrinous pleuritis. Bronchopneumonia of posterior portion of right lung. Early enterocolitis (?) with large, soft mesenteric lymph nodes. Acute splenitis. Fatty liver and kidney (both slight).

Nervous System.—Brain weight 1465 grams. Superficial asymmetry in minor sulci of cerebrum. Microgyria of right superior parietal lobule (no certain evidence of atrophy, but more flaring sulci; in particular the right parieto-occipital fissure is 1 cm. deeper and much wider than the left). Focal chronic fibrous leptomeningitis of right parieto-occipital fissure. Consistence of brain diminished (anterior poles least and lower surface of cerebellum less than upper surface).

Chemistry.—The water-content of three portions of the brain was determined in the chemical laboratory of the Harvard Medical School by Mr. J. B. Ayer, Jr., who found the following percentages: frontal region, 75 per cent; parietal, 77 per cent; cerebellum 82 per cent water. These findings parallel the consistence noted with the finger. The anterior poles were the least softened. The low percentage of water possibly indicates relatively high neuroglia content.

Case VI.—G. B., D. S. H., Nos. 11641, 3238, Path. No. 1149. Male, 57, single, carpenter. Born in Salem, Mass., of American stock. Was a case of dementia præcox, paranoid type, of perhaps 32 years duration.

Heredity.—Facts not known.

Previous History.—Was perhaps not "just right" from boyhood. Had certain delusions and may possibly have been suicidal early in life, but was shortly transferred after his first stay at Danvers to the Salem Almshouse, where he was quiet and industrious. Patient showed insomnia at times and had sensations of "sparks of fire" dropping on his head.

Readmitted January 1, 1904, with signs suggesting tuberculosis at both apices. A coarse tremor of extended tongue, a moderately fine tremor of extended fingers, and markedly exaggerated knee-jerks. Examination by Dr. H. W. Mitchell showed that the knee-jerks are usually followed by momentary clonus or tonic spasm of the leg followed by general body spasm, which does not seem to be always the same. The different movements depend upon the different postures of the body at the time the knee-jerk is obtained. Often the same body spasm can be gotten by a feint to strike the quadriceps tendon. Achilles reflex is prompt, but not much increased. It is followed, however, by various spasms of the legs, the most common being a tonic spasm of the muscles of the leg and thigh, often accompanied by irregular spasms of muscles of the trunk. *Triceps* and *biceps* prompt and lively and followed by irregular body spasms. *Cremasteric* and abdominal slight. *Plantar* very much increased, followed by tonic or clonic leg spasms. Usually no lifting of right toe. Rarely a suggestion of Babinsky reflex. The only physical stigma consisted in poorly-formed lobules.

Auditory hallucinations had been frequent for many years, always in the tones of attendants or other bystanders. There was one episode of visual, olfactory and gustatory hallucinations of an unpleasant character.

Very characteristic were patient's description of peculiar spiritualistic phenomena, with "forerunners and communications." Patient would often communicate with God, assuming a rigid position, gazing into space, and saying, "God, our Heavenly Father, I would like to communicate, if convenient, don't discommode yourself!" He pauses a few moments and then says, "Is that you? Is that you really, Heavenly Father? Please come as an apparition, as strong as you can." Then in a faint voice, "That's pretty good, pretty good. Can you come a little stronger, I wish you would if you could; that pretty good, that's good. God, Heavenly Father, is it safe to show the forerunner in the face of Dr. Mitchell? Are you sure, perfectly sure? All right." He would then make a peculiar movement of the hands which he alleges is a forerunner, and has the power of destroying life. Asked to forecast the future, he calls up God as previously, and says, "I wish to ask a question in regard to Dr. Mitchell's success in the future? Is your time precious, God? Can you spare it?" He turns to the examiner and says, "He is gone now to examine. He examines by astronomy." In the meantime, patient converses pleasantly about the weather until God calls, and later assures examiner that his success is to be unlimited, and that he has received communication. Result of these communications were, as a rule, optimistic.

Patient made characteristic, elaborative, decorative drawing, ostensibly for certain Masonic lodges. In 1905 certain slight mannerisms appeared, which later grew more frequent. He would wet his hands frequently, repeat certain muscular movements, shake his body, and make peculiar noises in his throat.

The patient died March 1, 1907, having been taken the day previously with vomiting and severe abdominal pains.

ANATOMICAL DIAGNOSIS (H. W. Mitchell and F. P. Gay).

Cause of Death.—Tuberculous enterocolitis with ulceration and perforation with localized peritonitis. Bacillus coli communis in heart's blood at autopsy.

Chronic Conditions.—Emaciation. Chronic fibrous pericarditis. Slight tricuspid valvular sclerosis. Chronic obliterative pleuritis (left) and chronic apical adhesive pleuritis (right). Disseminated tuberculosis of both lungs. Caseating mesenteric lymph nodes. Chronic pericholecystitis. Hepatic atrophy (especially left half of right lobe and all of left lobe). Chronic splenitis (marked).

Acute Conditions.—See cause of death. Acute nephritis.

Nervous System.—Brain weight 1490 grams. Generalized cerebral sclerosis (without visible atrophy). Occipital lobes firmer than rest of brain. Chronic fibrous leptomeningitis, confined to the superior frontal gyri. Cerebellum and spinal cord soft. Slight chronic external adhesive pachymeningitis.

CASE VII.—R. S., D. S. H., No. 11863, Path. No. 1168. Female, 24, single, a weaver by occupation. Born in Canada of French-Canadian parentage. Was a case of dementia præcox, hebephrenic type, of four years duration.

Heredity.—An aunt insane.

Previous History.—Of normal early development. Four years a weaver in Massachusetts. Deserted by lover at 20. Indifference and melancholy, auditory hallucinations, delusions of persecution, subjective sensations of heat. Occasional attacks of violence and refusal to be dressed followed.

Upon commitment, April 22, 1904, a slight tremor of tongue, slight albuminuria, and semi-adherent lobules were noted. Patient was quiet, usually mute, indifferent, occasionally irritable, and resistive. Patient lay in bed with clothes pulled over her head and would start up suddenly, rocking back and forth.

There was an apparent amnesia for recent and remote events. Auditory hallucinations, ill-defined delusions of persecution, a silly apathetic attitude persisted. Mutism developed later.

About a year after admission, signs of tuberculosis and physical failure set in, and 17 months after admission, signs of tuberculosis were detected and tubercle bacilli were found. Thereafter patient grew brighter and would occasionally sing, but would not talk and had to be tube-fed. The knee-jerks, normal on admission, were later lost (September, 1906).

The patient died May 4, 1907, about 14 months after onset of physical failure.

Anatomical Diagnosis (E. E. Southard).

Cause of Death.—Thrombosis of left common iliac vein and vena cava (unidentified organisms).

Chronic Conditions.—Malnutrition. Ascites. Hypertrophic cirrhosis of liver (2260 grams). Chronic adhesive pleuritis (both upper lobes). Bilateral phthisis pulmonalis. Bronchial lymph node tuberculosis. Brown atrophy of heart muscle. Slight mitral valvular sclerosis. Coronary arteriosclerosis. Chronic gastritis. Slight enlargement of right lobe of thyroid gland.

Recent Conditions.—See cause of death. Edema of left leg. Fatty changes in liver and kidney. Acute perisplenitis (extension from pleural process).

Nervous System.—" Brain weight 1105 grams. The cerebral hemispheres show no variety in consistence and suggest a slight softening of post-mortem origin. The convolutions are everywhere of the usual richness and appearance except that the upper two-thirds of the postcentral gyri appear narrower than normal, being scarce two-thirds the width of the precentral gyri. It is impossible to make out on section that the underlying white matter is firmer in the postcentral than the precentral gyri. The limits of this lesion cannot be made out exactly, and the lesion probably represents an anomaly of the postcentral gyri. Basal ganglia not remarkable. Weight of cerebellum, bulb and pons, 145 grams. The olives have the consistence of those of a normal brain. The right dentate nucleus is firmer than usual. There is a suggestion of thinning out of the laminæ in the clival and cacuminal regions.

Middle Ears.—Normal.

Spinal Cord.—Shows an increase of consistence in the lumbar region, and several segments at various points seem to show a thinning out of the anterior halves without, however, demonstrable diminution in the area of cross-section."

Case VIII.—J. O., D. S. H., No. 10862, Path. No. 1294. Female, 37, married, housewife. Born in Lynn, Mass., of Irish parentage. Was a case of mental disease, possibly dementia præcox, paranoid type, of six years duration.

Heredity.—Facts not known.

Previous History.—Patient was married at 23 and had four children, three girls and a boy. Nineteen days after the birth of the last child, which took place normally, except that both legs had been swollen, patient became noisy, thought she was dying and asked for the priest. She was carried to Lynn Hospital and was there excited and had auditory hallucinations. The left leg had swollen much worse 10 days after birth of child.

Upon commitment to D. S. H. June 5, 1902, this leg was still swollen and the skin scaling. The patient was confused and suspicious, at first tractable, later resistant, occasionally listening to imaginary voices, stating " they seem to speak from my hand." Delusions were sometimes somatic. When asked what was the trouble wth her, "It is like little bits of formed children. It makes me nervous." Pointing to the physician's note-book, she said, "That is not saints' work." Periods of violence with biting, kicking and scratching would alternate with quiet and agreeable periods. Food was refused. Ten days later the patient had become somewhat better and developed some insight, and about a month after admission was apparently recovered from hallucinations. Removed upon a visit by her husband, the patient again became depressed, apprehensive and confused. Heard "rappings" at night. Patient stated, "These things I am telling you are all lies, but I have got to say them, because I have that feeling and cannot explain. I feel as though someone was compelling me to go through with it. This person has a grudge against me." There was considerable variation in the development of hallucinations. Patient spoke of queer doings going on at the hospital and talked about seeing "four generations" walking out of the dining-room. Exceedingly active hallucinations developed again in November, 1902, and patient broke glass to reach her husband, who was being crucified. Patient became resistive, violent, profane; would then relapse into depression and confusion. Food was refused as unnecessary. In February, 1903, patient had become dull, would talk little, was occasionally resistive.

March 9, 1903, said, "When the sandbags came on the ward for the old lady with the fracture, the Lord said even the sandbag liked her because she had sandbags at the Lynn Hospital, and she used to go to the beaches too." Occasionally talked in a grandiose way about being St. Johanna. Occasionally struck patients without provocation, and would frequently run the length of the ward for no apparent reason. Patient often spoke of herself in the third person and often knelt in an attitude of prayer. While walking attempted to touch every tree. Patient began to refuse to dress and take care of her room. Conversation became loose and contained many meaningless phrases: "Why did you come here? You hear me and you know my reports as a queen. Yes, I am the queen of England. I was known as Mrs. Page in the hospital. The carriages and horses are all in my name. Do you deny it, Johnnie? Who do you mean? Nothing new. I have all my money invested. I have my own rights and places up there."

In 1907 the patient was transferred to the tuberculosis ward and there died December 14, 1908. Toward the close of life, knee-jerks had been exaggerated. There was apparent amnesia, and only partial orientation could be demonstrated.

Anatomical Diagnosis (A. H. Peabody and M. M. Canavan).

Cause of Death.—Phthisis pulmonalis and tuberculous enteritis with ulceration.

Chronic Conditions.—Malnutrition. Slight ascites, hydrothorax, and edema of ankles. Hydropericardium. Slight chronic fibrous endocarditis. Chronic obliterative pleuritis (right). Chronic apical pleuritis (left). Ovarian atrophy. Erosion of cervix. Tuberculous ulceraton of colon. Enlarged lymph nodes near cecum and along aorta. Cavitation of left upper lobe. Disseminated tuberculosis of right lung. Enlarged bronchial lymph nodes. Calvarium dense. Slight chronic external adhesive pachymeningitis.

Acute Conditions.—Acute nephritis.

Nervous System.—Slight chronic leptomeningitis with adhesions at frontal and temporal tips. Brain weight 1120 grams. Generalized increase of consistence of cerebrum (especially frontal and occipital), pons, and cerebellum.

Case IX.—J. W., D. S. H., No. 14591, Path. No. 1298. Female, 36, married, housewife. Born in Dracut, Mass., of Irish parentage. Was a case of dementia præcox, katatonic type, of about nine months duration.

Heredity.—Negative. One brother and one sister died of tuberculosis.

Previous History.—Healthy as a child. A good student, disposed to quick temper. Married at 25. Miscarriage at five months, followed by three boys and a girl. Became nervous and run down at 34 years.

Present Illness.—Onset of pain in right side about April 1, 1908. Several weeks later patient dropped her work complaining of "physical incapacity and pain in the chest." Insomnia and brooding followed and in June patient complained of having tuberculosis, but said she could not get well. After a vacation she began in August to worry more. She was once disposed to jump out of a window and several times stated that relatives were trying to cut her up. She feared poison in her food. There were spells of looseness of bowels followed by constipation.

Patient was committed to D. S. H. October 6, 1908. Partially adherent lobules of ears. Slight hypertrichosis of upper lip. Gothic palate. Teeth in poor condition. Atrophy of breasts. Expansion of right lung less than that of right. Slight resistance of passive movements. Upon admission patient chiefly lay in bed as a rule with her eyes full of tears, moved very slowly and expressed the idea that every one was trying to hurt her. Patient's emotional reactions were very slight, although stating that deep palpation of the abdomen hurt her. Her expression gave no signs of pain. Although describing fear of being hurt, she gave no further evidence of fear. At first appeared depressed and retarded, she later improved. Had a spell of untidiness, became more active, gave irrelevant replies, and showed inertia suggesting dementia præcox. The diagnosis of manic depressive insanity, depressed phase, was first made, largely based on retardation in conversation and movements. In the middle of December, 1908, patient again became untidy and sat on floor; showed certain physical failure. Her conversation was limited largely to "I want to go home." Without definite proof of tuberculosis, she was placed in the building for tuberculosis, and there showed restlessness, negativism, a tendency to pulling bed clothes from other patients and untidiness. There were several slight rises of temperature. January 7, 1909, patient had a severe generalized convulsion, after which time she lost weight, became unable to speak and to swallow easily. She mentioned slight headache in the last few days of her life. Death January 16, 1909.

Anatomical Diagnosis (M. M. Canavan and C. G. McGaffin.)

Cause of Death.—Ileocolitis with ileac ulceration. Infection of cerebrospinal fluid with organism resembling bacillus of fowl-cholera.

Chronic Conditions.—Malnutrition. Sacral and trochanteric decubitus. Teeth poor. Gastroptosis. Chronic perisplenitis. Chronic periappendicitis. Chronic adhesive apical pleuritis. Slight chronic parietal endocarditis. Mitral valvular sclerosis. Small vegetation of aortic valve. Slight aortic sclerosis. Tuberculosis of apices. Slight cirrhosis of liver with fatty change. Chronic purulent cholecystitis. Laceration of cervix. Chronic external adhesive pachymeningitis over vortex.

Acute Conditions.—Tumor of left kidney. Acute nephritis (pyelo nephritis?). Acute endocervicitis. Thrombus of left internal iliac artery. Uulcers of ileum. Injection of jejunum, ileum, colon and rectum.

Nervous System.—Pia faintly injected and adherent to dura over left middle frontal in an area 1 x 1 cm. in diameter, 16 cm. from tip of pole. Pia is raised from the brain by a clear fluid over the vertex region. Pia slightly cloudy over vessels, but strips from cortex smoothly. Hemispheres equal in size and in general slightly firmer than normal. The left second temporal convolution is more prominent than others of its side or the opposite temporal convolutions. The left precentral gyrus measures on mesial aspect 2 cm., left postcentral 1.5 cm. The right precentral measures on mesial aspect 5 cm.; the right postcentral 1 cm. Sulci around right postcentral gaping. Cut sections show the postcentrals to have faint and thin grey matter and their white matter shrinks from the knife. The ventricles are smooth. Ganglia normal. Basal vessels not notable. Sections of the brain show no further gross lesions.

Brain weight 1300 grams. Pons and cerebellum 190 grams.

Middle Ears.—Gasserian ganglia and cord not notable.

Case X.—M. M., D. S. H., Nos. 2874, 11624, Path. No. 1303. Female, single, 55, compositor. Born in Peabody, Mass., of American parentage. Was a case of dementia præcox, observed in a terminal stage.

Heredity.—An uncle insane at D. S. H.

Previous History.—Patient was admitted to D. S. H. with diagnosis of chronic mania (duration six months) June 6, 1883, and was discharged unimproved to Salem Almshouse August 28, 1885. At 29 believed she was a clairvoyant; apparently had auditory hallucinations. Complained of pains in throat and constantly spitting blood. "Could feel other people's injuries." Excitement on admission; assumption of absurd attitudes and declamation. Disconnection on talk. Made mysterious mention of Masonic signs. More active delusions brought out by menstruation. Her delusions dealt chiefly with injuries brought upon others which she could feel. At Salem Almshouse the dementia advanced. She had a vagrant tendency and was resistive.

Upon second admission to D. S. H. January 4, 1904, patient showed a heavy growth of hair on chin and upper lip; a narrow high palate and slight arcus senilis. Exaggerated knee-jerks, continuous tremor of lips, slight lingual tremor, inconstant tremor of hands, slight peripheral arteriosclerosis, and signs of aortic valve sclerosis. Mentally, patient talked disconnectedly in answer to questions. Failed to occupy herself in any way; wore an unchanging facial expression. Claimed to have been dead and reborn many times. Persistently stated that she bore another name than her own and showed an apparent defect of memory for both recent and remote impressions. Was unable to make her way about the ward. Sample of conversation: "We don't know whether it is Heaven or earth we are sitting in. The house feels such a move. It moved right along this morning like a train. You were marked when you came in." Do you hear voices sometimes? "I hear the occupants of another world." Do you have any thoughts? "When I read books." Do you read books? "Sometimes. I believe I am a baby with all these attacks." What attacks? "The attacks, points, and scoops." Are you out of your mind? "You have got to pray to God to get out of this building. My father told me I would be the Lord's wife. He told me to obey my husband and my Lord." How long have you been married? "I can't tell, a number of years. I have been a baby since I have been married."

Again, Why were you sent here? "Because I pushed the bed back and a bullet came through the wall. I was chewed and born and clambered and went through shambles." Why were you sent here? "Because there were so many thieves around." What did you do? "I started my nun work and read my Bible in my room, thank God and all God."

Patient at Middleton Colony restless and vagrant. In last few months the patient grew careless of dress and showed mannerisms, stereotyped movements, resistiveness and severe Bright's disease. Death February 16, 1909.

ANATOMICAL DIAGNOSIS (A. H. Peabody and C. G. McGaffin).

Cause of Death.—Chronic diffuse nephritis and acute bronchitis.

Chronic Conditions.—Malnutrition. Slight sacral decubitus. Aortic valvular sclerosis (foci of calcification). Slight aortic sclerosis. Coronary arteriosclerosis. Dilated stomach. Chronic diffuse nephritis. Chronic perisplenitis. Mural and subperitoneal fibromyomata of uterus. Atrophy of ovaries. Calvarium dense. Exostosis of frontal bone. Adherent dura. Chronic tympanitis auris. Calcification in falx cerebri.

Acute Conditions.—Acute bronchitis. Slight enlargement of mesenteric lymph nodes. Abrasions of forehead and left hand.

Nervous System.—Brain weight 1220 grams. Chronic fibrous leptomeningitis of vertex, along sulci at base of brain and over cerebellar cisterna. Generalized increase of consistence of brain. Pigmentation of cerebral grey matter.

CASE XI.—E. F., D. S. H., No. 13582, Path. No. 1310. Female, 28, single, mill operative. Born at Manchester, N. H., of Scotch-Irish parentage. Was a case of dementia præcox probably of hebephrenic type, possibly, originally imbecile. The total duration of the dementia præcox features was perhaps four years.

Heredity.—Facts unknown. Insanity in family denied.

Previous History—Patient always of subnormal mental capacity. "Peculiar, stupid, and ugly." Dull and backward at school. Worked steadily in a mill, but never saved money. Was sullen and cranky. At 24 years irritability, indolence, untidiness, aimless wandering and increasing silliness set in. A tendency to gluttony. The police often picked her up on the street at night.

Patient was admitted to D. S. H. April 5, 1907. Adherent ear lobules. High arching palate. Acne eruption. Gait peculiar, at times normal, at times patient swings one foot in front of the other and totters back and forth (mannerism?). Occasionally turns and twists her fingers about in a stereotyped way, touching objects with finger tips. Knee-jerks exaggerated. Patient smiled and grinned, was untidy, and habitually lay in bed with clothes over her head. Patient mute except on repeated questioning, when an occasional "yes" or "no" could be elicited. Later patient became more tidy and again untidy. Patient was apparently not oriented while in hospital and showed amnesia and defective impressibility.

Developing fever in November, 1908, she was transferred to the tuberculosis building, where she grew weaker and died March 22, 1909.

ANATOMICAL DIAGNOSIS (C. G. McGaffin and N. B. Burns).

Cause of Death.—Phthisis pulmonalis.

Chronic Conditions.—Malnutrition. Unequal pupils. Asymmetry of thorax. Marked mitral sclerosis. Hypertrophy of left ventricle. Hydropericardium. Chronic adhesive pleuritis of anterior portion of left lung. Tuberculosis, with cavitation of left lung, and slightly of right lung. Enlarged bronchial lymph nodes. Chronic passive congestion of liver. Dextroflexion of uterus. Thyroid gland small. Cyst of left Fallopian tube.

Acute Conditions.—Thrombosis of left auricle, staphylococcus septicemia.

Nervous System.—Gliosis of both frontal regions. Atrophy (or aplasia?) of left postcentral gyrus. Left precentral gyrus broader than right. Brain weight 1300 grams.

CASE XII.—M. C., D. S. H., No. 12143, Path. No. 1317. Female, 44, single, mill operative. Born in Ireland; father English, mother Irish. Was a case of dementia præcox of paranoid type of 21 years standing.

Heredity.—Father intemperate.

Previous History.—Patient a woman of ordinary mental capacity. Limited education; of melancholy and reserved tendency. Attack began at 23 with insomnia and anorexia, followed later by auditory hallucinations, fear, desire to become a nun, and wandering tendency.

On admission to D. S. H., October 25, 1897, the diagnosis of primary dementia was made. Patient was resistive, repeating, "Oh, my God protect me." Had auditory hallucinations and various delusions, sometimes religious. Mutism, refused to eat, restlessness, later increased stupidity, untidiness, and troublesome activity. In 1890 patient was able to work in the laundry, but in 1893 became quarrelsome and violent, often laughed in meaningless fashion and could not be prevailed upon to answer questions. Removed to Lawrence Almshouse June, 1893.

Recommitted to D. S. H. August 31, 1904. Patient sat about idly talking to herself or laughing in a silly manner and if permitted would wear four or five aprons. Her speech was peculiar and babyish and many replies were in whispers. Disorientation was apparently complete. Memory for recent and remote events was poorly preserved. Grimaces and various mannerisms. Patient would for long periods sit about listlessly and then become talkative. At times patient became quarrelsome; noisy at night and resistive.

Cancer of left breast was noted in July, 1908. Operation November 30, 1908. Had no effect on mental state. Death from metastases May 19, 1909.

ANATOMICAL DIAGNOSIS (A. H. Peabody and M. M. Canavan).

Cause of Death.—Multiple metastatic carcinomatosis.

Chronic Conditions.—Inequality of pupils. Edema of ankles. Brown atrophy heart muscle. Slight coronary arteriosclerosis. Chronic periappendicitis. Chronic adhesive pleuritis. Lateral misplacement of uterus. Chronic gastritis. Surgical removal of left breast (carcinoma). Carcinoma of axillary lymph nodes, left lungs, bronchial lymph nodes, and liver.

Acute Conditions.—Icterus. Hemorrhagic conjunctivitis. Hemorrhagic endometritis. Acute nephritis. Hypostatic pneumonia.

Nervous System.—Adherent dura. Chronic fibrous leptomeningitis, along sulci. Cervical spinal cord firm. Brain weight 1210 grams.

CASE XIII.—M. K., D. S. H., No. 14597, Path. No. 1319. Female, 31, married, mill operative. Born in Ireland. Was a case of dementia præcox of the paranoid type (possibly imbecile) of eight years duration.

Heredity.—Sister epileptic.

Previous History.—Poor scholar and truant in convent school in Ireland. House work and mill work after coming to America at 15. Married at 18; three children, followed by separation. Illegitimate child at 23. An attempt at suicide is asserted at 23-24. History before commitment is limited. Insomnia and street-walking are reported.

Commitment to D. S. H. October 10, 1908. Slight coarse tremor of fingers and tongue. Patient dull and apathetic. Lay quietly in bed looking at one point on ceiling as if hallucinated. Orientation imperfect. School knowledge and calculating ability deficient. Memory somewhat impaired for remote events; still more impaired for recent events. It later transpired that she could see the Virgin Mary at any time. Patient at times sang religious strains. Muscular movements were in general slow and languid. She was apt to assume attitudes suggesting those of saints in religious pictures. Once she betrayed a fear that men were after her. In January, 1909, she had become at times resistive and fearful. She was tube-fed several times. At times patient stated that she had a bad taste in her mouth.

Died May 28, 1909, of colitis.

Anatomical Diagnosis (A. H. Peabody and M. M. Canavan).

Cause of Death.—Acute follicular colitis.

Chronic Conditions.—Malnutrition. Inequality of pupils. Edema of ankles. Ascites. Chronic adhesive pleuritis, left. Chronic fibrous pericarditis. Chronic fibrous endocarditis. Aortic sclerosis. Tuberculosis of left apex. Chronic perisplenitis. Renal arteriosclerosis. Chronic diffuse nephritis. Slight cirrhosis of liver. Chronic endocervicitis. Calvarium dense.

Acute Conditions.—Acute nephritis. Acute jejunitis, ileitis and colitis. Acute proctitis. Acute vaginitis.

Nervous System.—Cervical spinal cord large. Slight chronic leptomeningitis especially basal. Brain weight 1250 grams.

Case XIV.—F. O., D. S. H., Nos. 8471, 13648, Path. No. 1335. Male, 32, single, shoemaker, born in Lynn, Mass. Father born in Massachusetts; mother born in Nova Scotia. Was a case of dementia præcox, katatonic type, of 20 years duration.

Heredity.—Paternal grandfather alcoholic.

Previous History.—At 12 years an attack of confusion and more or less unconsciousness lasting two weeks. Pains in back and head at intervals for years. At 18 years spells of laughter and boisterousness, delusions of being mesmerized, elation and depression spells, insomnia, threats of violence and suicide.

On commitment to D. S. H., October 23, 1896, patient was talkative and expressed numerous delusions and pseudoscientific theories. "The moon is the blind eye of some animal. There is a change every thousand years, so the men of a thousand years ago are now women, and *vice versa.* The reason why the Egyptians are so small is because he put vitriol into them a thousand years ago, and it is all described in the inscriptions. He has the shoulders of an Egyptian, the head of Napoleon or an Italian, and his limbs are French. We are all being continually acted upon by minerals, herbs, electricity, and magnetism, and one person's brain acts directly upon another's."

The physical condition was well maintained. There was a progressive apathy, with occasional noisy spells and unprovoked assaults on patients. In 1898 assigned historic parts to officers: head supervisor was Mrs. Grover Cleveland, superintendent was Napoleon, the pathologist was Daniel Webster, etc. Much profane, obscene and foolish talk.

Later, patient was habitually found mumbling and laughing foolishly on a settee. Eczema of buttocks and scrotum from dribbling of urine. Dysentery in September, 1904. The urine then began to show albumin.

Patient's apathy occasionally gave place to excitement, denudative spells, and the expression of extravagant delusions.

Transferred to Foxboro State Hospital March 5, 1907. Readmitted to D. S. H. May 10, 1907. Untidy, manneristic, with tendency to hold fixed positions. Placed in tuberculosis building in 1908, where he had spells of noise-making. Diarrhœa set in in July, 1909, but there was no blood or mucus in the stools. Toward the close, patient could not keep a straight line in walking. Patient's characteristic position was similar, lying, standing, and walking, and consisted in a curled-up stoop with arms folded over abdomen.

Death suddenly, after a gradual exhaustion, August 21, 1909.

Anatomical Diagnosis (M. M. Canavan and A. A. Hornor).

Cause of Death.—Phthisis pulmonalis. Intestinal obstruction.

Chronic Conditions.—Malnutrition. Dilatation of pupils, oval from above downwards. Scaling and pigmentation of skin. Chronic focal adhesive peritonitis. Chronic adhesive apical pleuritis (left). Hydrothorax (right). Heart small (145 grams). Slight chronic fibrous endocarditis (left ventricle). Tuberculosis of apex of left lung. Tuberculosis with cavitation of right lung. Liver weight 940 grams. Cystitis and prostatitis. Slightly adherent dura. Chronic tympanitis auris (left).

Acute and Recent Conditions.—Intestinal obstruction. Acute jejunitis and ileitis. Mesenteric lymphnoditis. Acute nephritis.

Nervous System.—Spinal cord small. Chronic leptomeningitis along sulci of vertex, in Sylvian fissures, and at base of brain. Thrombi of superior longitudinal and left lateral sinuses.

Case XV.—M. D., D. S. H., Nos. 10098, 10580, Path. No. 1358. Male, 24, single, shoemaker. Born in New Brunswick of Irish-Canadian parentage. Was a case of dementia præcox, katatonic type, of 10 years duration.

Heredity.—Unknown. Orphan.

Previous History.—Two years before commitment, malaria with refusal to talk (patient's statement). Normal to 15 years, of average school capacity. Ten days before commitment patient had spells of crying, jumping, shouting, and incoherent talk, with refusal of food for about a week. Patient believed he had appendicitis. Urine was drawn with catheter four or five days before commitment. Headache during two nights before commitment.

Commitment D. S. H. September 15, 1900. Nose asymmetrical. Malnutrition. Depression explained by patient as due to lack of sleep, having no mother and lack of appetite. Patient was dazed and bewildered, refused food, was at times normal, later mute, untidy, resistive. The katatonic symptoms then diminished, and patient could be got to take food. Periods of mutism and fixed attitudes alternated with brighter and more responsive periods. Late in 1900 he had become apathetic, but worked in the dining-room, occasionally noisy and mischievous. Tonsillitis in March, 1901. Weight and physique had in general much improved. Active symptoms then almost wholly ceased, and patient was discharged April 1, 1901.

After discharge, patient worked well in shoe shop and drove team acceptably to employers. On being taken to learn a trade in Boston, August, 1901, he stayed but two weeks, and returned erratic, boastful, profane, threatening, and was recommitted October 12, 1901, in approximately perfect physical health.

As a rule surly and profane, patient was sometimes tractable (November

1901; February to July, 1902; September to January, 1903). Occasionally untidy. Often restless, sleepless, and annoying to helpless patients. A second attack of follicular tonsillitis September, 1902.

April, 1904, confusion, peculiar way of putting on clothes, swaggering about, mutism or incoherent responses to questions, facial grimaces, twitching of facial muscles. November and December, 1904, orderly and tractable, though apathetic, correspondent with an attack somewhat suggestive of typhoid fever (positive Widal reaction in second week).

During 1905 and 1906, patient was apathetic, idle, properly oriented, and had very good memory.

In the spring of 1906 patient grew depressed and unwilling to eat, became untidy, mumbling, and disoriented, and during July and August became restless, excited, given to running about making peculiar movements and assaulting helpless patients. A period of quiet dulness followed.

Patient's weight increased; he was given parole privileges.

In February, 1909, patient grew despondent and untidy, often refused food, and took to continual praying. In August dysentery set in, with persistent diarrhœa; mutism and occasional prayers.

Sudden collapse set in on November 18, 1909. Death. Patient mumbled a few words to physician on day of death.

ANATOMICAL DIAGNOSIS (H. M. Adler and M. M. Canavan).

Cause of Death.—Acute ulcerative ileocolitis (bacillary dysentery).

Chronic Conditions.—Malnutrition. Unequal pupils. Trochanteric decubitus. Chronic appendicitis. Chronic obliterative pleuritis (right). Obsolete tuberculosis of left apex. Chronic perisplenitis. Chronic gastritis. Cystitis (thickened wall). Calcification of lymph node near pancreas. Calvarium thick. Slightly adherent dura mater.

Acute Conditions.—Acute ileocitis. Enlargement of mesenteric lymph nodes. Acute bronchitis (right). Acute splenitis. Fatty changes of liver and (slight) kidneys.

Nervous System.—Sclerosis of left inferior frontal gyrus. Brain weight 1200 grams. Slight chronic fibrous leptomeningitis. Lumbar spinal cord soft.

In seeking for correlations in these data, let us first inquire how many of the lesions described can safely or probably be regarded as congenital anomalies or lesions acquired long prior to mental change. For a proper judgment here we shall need to take into account not merely the lesions in question, but the total clinical and anatomical impression presented by each case.

I, 840. A woman of Irish extraction, a capable school-teacher for 13 years, developed at 35 after over-work, a depressed, delusive, languid state, upon which typical katatonic symptoms shortly supervened, and died of phthisis at 37. Possibly the brain was somewhat atrophied, but not visibly so, save in the frontal regions. Although visible generalized atrophy cannot be asserted, there was a palpable generalized gliosis. (*Acquired.*)

II, 991. A Nova Scotian carpenter, given to frequent masturbation and later to excess in venery, developed a mental disease at 24 variously diagnosed in different State hospitals as "hypochondriacal paranoia," "chronic melancholia," "neurasthenia," is said to have threatened suicide, complained of pain, abnormal sensations ("brain and legs whirling round"; "I can't speak, because it pulls down and up and wound around me"—making motions from abdomen to neck), was hypochondriacal, eventually answered only in monosyllables, developed tuberculosis and died at 35. Slight generalized cerebral gliosis, without visible atrophy. (*Acquired.*)

III, 1034. An Italian immigrant, for 10 years a shoe operative of average capacity, somewhat easily affected by alcohol, developed at 33 auditory hallucinations and persecutory delusions, later grew dull, reticent, given to impulsive acts, and then showed echopraxia, cerea flexibilitas, mutism, at times automatism; died of pulmonary gangrene at 35. A kind of simian hirsuteness and hypoplasia of heart and aorta perhaps suggest "degeneracy." The pupils also were unequal and one was oval. The brain of this case was of good weight, and the solitary lesion it showed was a sclerosis and pigmentation of the dentate nuclei of the cerebellum. (*Acquired.*)

IV, 1062. An Irish housewife, who had borne three children, was deserted by her husband and developed at 28 somatic delusions, depression, and suicidal tendencies. On commitment signs of tuberculosis of both apices were discovered, which tuberculosis was fatal 10 years later. Full of delusions, abusive, noisy, obscene, the woman never showed katatonic signs unless reticence and a single period of mutism can be so interpreted. The brain of this case was of proper weight and showed palpable gliosis (without visible atrophy) of the superior frontal, prefrontal, and orbital gyri. At death (38 years) the genitalia were already atrophic. There was an aberrant thyroid. (*Acquired.*)

V, 1137. An Irish shoe operative (father possibly alcoholic) developed loose delusions of influence and a little later peculiar motions and gestures, mutism, stereotyped movements. All these symptoms, except mutism, ceased in later years. The total process lasted 15 years and the man died at 35. As in Case II, both heart and aorta were small. One testis was atrophied. The brain weighed 1465 grams and showed a striking microgyria of the right parietal lobule. Whether this lesion is acquired or aplastic would be hard to decide on anatomical grounds, but there was a focus of chronic pial change in the adjacent parieto-occipital fissure. There is a suggestion of sclerotic changes in the frontal regions and the lower surface of the cerebellum. (*Acquired? Congenital??*)

VI, 1149. A carpenter, hyper-religious, and given to spiritualism, perhaps never "just right," has episodes of auditory, visual, olfactory, and gustatory hallucination (possibly also tactile), but during a quiet course of 32 years eventually settles into habitual, apparently voluntary, "communications" with God. Certain tremors, of doubtful interpretation, partly voluntary, were at one time evident in reflex tests. Characteristic mannerisms were late in appearing (55 years) and were then slight. Death at 57. The brain showed a generalized increase in consistence (without visible atrophy) and especially firm occipital regions. There was no palpable sclerosis of the frontal regions, but there was a regionary chronic leptomeningitis. (*Acquired.*)

VII, 1168. A French-Canadian woman, of normal development and a weaver for four years, after desertion by lover, developed auditory hallucinations, persecutory delusions, certain subjective sensations, and resistivism, later apathy, mutism and less of knee-jerks. Death four years after onset, at 24 years. The brain weighed 1105 grams and showed an atrophy (or aplasia) of both post-central gyri, a mild sclerosis of the right dentate nucleus, and possibly other slight chronic cerebellar lesions. (*Acquired, Congenital?*)

VIII, 1294. An Irish housewife, who had borne four children, developed swelling of both legs at her fourth confinement and 19 days after birth of child became boisterous, fearful of death, and had auditory hallucinations—thrombosis of left leg had set in. Auditory hallucinations, delusions of suspicion, and periods of violence gave place to virtual recovery. At home recurrence of hallucinations, followed in the hospital by violence, resistiveness, refusal of food, later apathy. Impulsive movements, frequent genuflexion, employment of third for first person, stereotyped movements. Death after six years at 37. Generalized slight cerebral sclerosis, especially frontal and occipital. Slight focal leptomeningitis, frontal poles and tips of temporal lobes. Atrophy of ovaries. (*Acquired.*)

IX, 1298. An Irish housewife, who had borne four children, developed pains, insomnia, ideas of suicide, fear of tuberculosis, delusions of poisoning. On commitment, hypertrichosis of upper lip and atrophy of breasts had set in. The palate was Gothic. The symptoms first suggested the depressed phase of manic-depressive insanity. Apathy, negativism, untidiness, followed a severe generalized convulsion nine days before death (nine weeks after onset, 36 years). Brain of proper weight. Atrophy (or aplasia?) of postcentral gyri. Gliosis of left second temporal gyrus. (*Acquired? Congenital.*)

X, 1303. A woman compositor of New England parentage (uncle insane) believed at 29 that she was clairvoyant and apparently had auditory hallucinations as well as somatopsychic delusions, possibly based on hallucinations. Apathy, peculiar autopsychic delusions toward death, carelessness in dress, mannerisms, stereotypy, resistiveness. Course of 25 years. Death at 55. Generalized increase of consistence of brain, with pigmentation and a chronic leptomeningitis of the vertex, along sulci, at the base, and over cisterna cerebellaris. (*Acquired.*)

XI, 1310. A Scotch-Irish mill-worker, a woman always of subnormal mental capacity, developed at 24 a pronounced change of character with hebephrenic features. In hospital mannerisms or peculiarities of gait, certain mannerisms of finger movements, and virtual mutism. Unequal pupils. High palate. Asymmetry of thorax. Death at 28. Small thyroid gland. Frontal lobe gliosis. Atrophy or (aplasia?) of left postcentral gyrus. (*Acquired, conegnital?*)

XII, 1317. Woman, mill-worker (father alcoholic), at 23 had insomnia, followed by auditory hallucinations, fear, religiosity, vagrancy. In hospital, resistive, hallucinated, delusive, mute, refusing to eat; later violence. Finally apathy, with manneristic speech and grimaces. Death from carcinomatosis, 21 years after onset. Occipital microgyria. Chronic leptomeningitis along sulci. Cervical spinal cord firm. (*Acquired.*)

XIII, 1319. High-grade imbecile. Irish mill operative. Sister epileptic. Mother of three children and a fourth illegitimate. One attempt at suicide. Eight years' course with onset at 23. Religiosity. Could see Virgin Mary at any time (hallucination rather than delusion). Imitation of saints' attitudes as seen in pictures. Possibly gustatory hallucinations. Death at 31. Unequal pupils. Cervical spinal cord unusually large. Slight leptomeningitis, especially basal. (*Acquired and congenital.*)

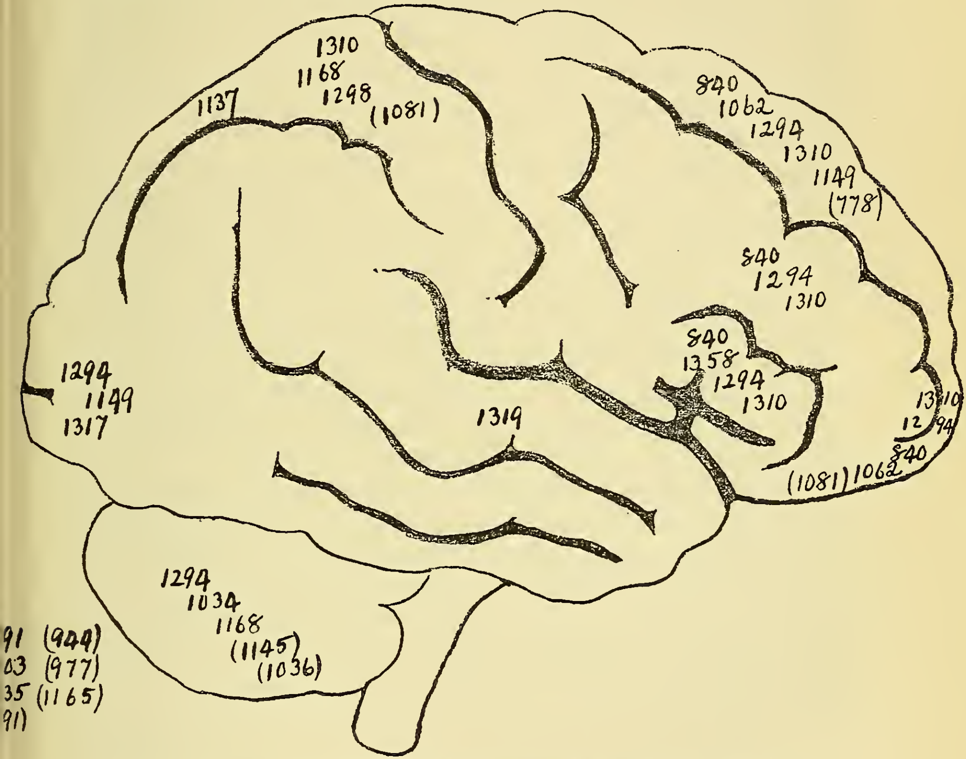
XIV, 1335. Shoe operative. Attack of doubtful character at 12 years. Paranoid symptoms began at 18. Katatonic symptoms gradually supplanted the paranoid. Death at 32. Spinal cord unusually small. Brain weighed 985 grams, but was apparently not to any great degree atrophied. Heart (145 grams) and liver (945 grams) also small. (*Congenital.*)

XV, 1358. Irish-Canadian, shoe operative. Onset at 15. Katatonic, later apathetic, then apparently recovered (seven months after onset). Recurrence four months later. Remarkably periodic course. Death at 24. Palpable sclerosis of the left inferior frontal gyrus. Slight chronic fibrous leptomeningitis. (*Acquired.*)

One's superficial judgment, therefore, concerning the origin of the lesions in question is that they took rise in the adult brain in 840, 991, 1034, 1062, 1149, 1168 (at least in part), 1294, 1303, 1310 (at least in part), 1317, 1319 (in part), 1358=12 cases, possibly also in 1137, 1298=maximum of 14 cases. So far as 1335 is concerned (Case XIV), it might well be doubted whether the hypoplastic nervous system formed more than a nidus for the mental process; perhaps this case should be put in the macroscopically normal group.

It is but fair to insist, on the other hand, upon the congenital features. Besides 1335, 1137, 1168, 1298, 1310, 1319, gave rise to a suspicion of congenital features in the nervous system alone =6 cases. And, if we add anatomical features outside the nervous system, then 1034 (hirsuteness, hypoplasia of heart and aorta) 1062 (aberrant thyroid) might be added=a maximum of eight cases probably or possibly in part provided with congenital features.

It appears, accordingly, that, although congenital features are not absent from our group, there is strong color for the provisional judgment that numerous acquired lesions of the nervous system exist in our series.



Focal Atrophies, Aplasias, or Scleroses in Dementia Præcox.
() indicate microscopic evidence only.

The Pre-Rolandic Group.

The frontal region was specially marked out for injury (whether acquired or congenital is for the moment not considered) in cases 840, 1062 and 1358; was prominently injured also in 1294 and 1310; and obviously shared to some degree in the generalized mild injury which was macroscopically made out in 991, 1135, 1303, and in 1335 (unless this brain be regarded as showing hypoplasia of congenital origin), *i. e.*, in at most nine cases.

Consider first the three cases in which the macroscopic lesions specially affected the frontal region. 840 was at first paranoid, then shortly katatonic. 1062 was paranoid, perhaps never katatonic. 1358 was a katatonic case with remarkable remissions. At first sight it seems hopeless to seek clinical correlations in these cases. But, bearing in mind the conclusions of Campbell and Brodmann concerning the histological differentiation of the so-called frontal region into subdivisions, it is clear that we cannot demand close clinical correlations here.

As a matter of fact, the lesions of 840 (the case with paranoid-katatonic course) involved, so far as eye and finger could determine, the *whole* of both frontal regions, and the whole brain itself showed a generalized increase of consistence. Whatever the relation of the patient's brain disease to her symptoms, there is not the slightest doubt that the patient had been subject to a sclerosing brain disease of mild but generalized character during the last years before death (assigned duration three years). Microscopically, the gliosis of this case was generalized and not demonstrably severer in the infrastellate layers.

But, though the changes of 840 are too severe and wide-spread and the symptoms too mixed for correlation, the same is not true of 1062 (paranoid, perhaps never katatonic). A woman of the same age as 840, but with a much longer assigned duration of symptoms (11 years or more) and with alcoholism clouding the issue, 1062 had maintained proper brain weight and showed gliosis confined (so far as macroscopic examination could determine) to the superior frontal, prefrontal, and orbital gyri, *i. e.*, to a continuous area probably containing but two histologically separate cortex-types. It is perfectly true that microscopic examination shows a degree of the same process (gliosis, satellitosis) in other regions, so that here again the brain cannot be freed from the suspicion of a generalized change. Still both macroscopic and microscopic examinations seem to prove that the superior frontal and prefontal cortex is subject to the most severe and possibly to the oldest process of injury. It becomes, therefore, at least a working hypothesis for this case to consider the paranoid symptoms as related with lesions in the superior frontal and prefrontal regions.

But what kind of interpretation is left open for the purely katatonic case, 1358? The analysis of this case is still far from complete. The greater part of both frontal regions was, as a matter of fact, wholly spared from macroscopic lesion. Only the left inferior frontal gyrus was affected, presenting an induration of an isolated and distinct, though mild, character in the midst of an otherwise apparently normal brain (slight general leptomeningitis). What relation, if any, this particular lesion bears to the katatonia of this (clinically somewhat unusual) case, is impossible to say; but it is certain that the data of 1358 do not controvert in any respect the correlations suspected for 1062 (the practically pure paranoid case) or even for 840 (a clinically more rapidly progressive and mixed case), as the macroscopic distribution of the lesions indicates.

The other frontal lobe cases deserve brief mention. The distribution of the lesions in 1294 is in consonance with the progressive paranoid-to-katatonic character of the disease: the case resembles in some respects 840 (just considered); but its duration is longer (six years) and the katatonic symptoms were much delayed in their development. The brain had undergone a mild generalized sclerotic process (widely distributed gliosis microscopically) which had especially affected the frontal and occipital parts of the brain and included the cerebellar cortex and even the pons. The frontal tips actually showed a few pial adhesions (a rare event outside of general paresis and other exudative or post-exudative lesions). The extent of this prefrontal process again recalls 840; but the whole case is obviously too complex, progressive, and longstanding to permit more than a suspicion of the course of cortical events.

1310 is best considered below among complications of the post-Rolandic group: it showed both delusions and katatonic symptoms, but was at first pronouncedly hebephrenic.

The group of generalized glioses (without defined gross atrophy) here considered numbers three. One of these (991) was practically paranoidal throughout its 11-year course, and, as a matter of fact, microscopically showed a marked superior frontal lobe gliosis (with satellitosis); but the case is clinically not too clear, and no deductions need be risked therefrom.

Another generalized gliosis, 1303, was apparently the end-stage of a hebephrenic, with a disease of 25 years' duration. Correlations are impossible. Histologically, there were marked gliosis and satellitosis, especially of deeper layers.

1335, the last of this group, is very possibly an instance of hypoplasia or of arrested development of the brain. The brain at autopsy weighed but 985 grams (heart 140 grams, liver 940 grams). Correlations here also are difficult.

Before dismissing the pre-Rolandic group, 1149 may be considered in this connection. I have placed 1149 provisionally in the post-Rolandic group largely on the basis of the well-defined occipital gliosis; but the brain showed a generalized sclerosis (microscopically marked, with some degree of satellitosis in places). The reason for possibly including it, more especially, in the frontal group is the occurrence of chronic fibrous lepromeningitis, confined to the superior frontal gyri. The case was clinically a supreme example of a paranoid dementia præcox of 32 or more years' duration, and with certain katatonic symptoms appearing very late in life.

The above sketch of the features of the pre-Rolandic group leaves us with the suspicion that paranoid cases begin with lesions striking especially the frontal tips and the superior frontal gyri. Cases with katatonia supervening later and with a progressive course of greater duration show involvement of other regions or even of the whole brain.

The Post-Rolandic Group.

(a) Cases 1137, 1168, 1298 and 1310 (also frontal) form a sub-group which might, perhaps, be termed sensory-perceptual. (b) Cases 1149 and 1317 are cases of occipital lesion, 1319 of superior temporal lesion.

(a) The postcentral-superior-parietal or sensory-perceptual group of cases claim attention as exhibiting lesions in a region doubtless of great importance in interpretation of sensory impulses. All four of the cases were alike in developing katatonic symptoms.

1137 began, it is true, with a delusion, but a peculiar one (electrification), possibly due to sensory misinterpretation: thereafter the patient developed katatonia, demented seriously, and died (15 years' duration). The visible atrophy (or aplasia) in the right superior parietal region, accompanied by microgyria and a dense local deposit of fibrous tissue, formed a striking local lesion. At the time of death, however, gliotic changes with satellitosis had become widespread. Purposely I avoid discussing whether the focal lesion is acquired or congenital and what its pathogenesis may be, since for the time being the topographic distribution of such lesions is the important consideration.

1168 showed at autopsy what looked like a bilateral anomaly—a hypoplasia of both postcentral gyri in their upper two-thirds. The onset in this woman occurred at 20 after desertion, and katatonic symptoms were admixed with persecutory delusions and subjective heat-sensations almost at the start. The course was katatonic thereafter.

1298 pursued an acute course of katatonic character with death after nine months. The brain showed, besides double postcentral gliosis in the white matter and visible atrophy of the right postcentral gyrus, a peculiar focus of duropial adhesions over the left middle frontal gyrus. This case was at one time diagnosed as depressed phase of manic-depressive insanity.

1310 appears clinically to show a marked imbecilic strain. Perhaps the left postcentral atrophy and the precentral inequalities are largely of congenital derivation. The frontal gliosis is consistent with the imbecilic or hebephrenic cast of the case. Numerous katatonic features developed.

The sensory-perceptual sub-group, as represented by these cases, shows lesions which lead to the suspicion, if not the proof, of congenital anomalies. Symptomatically these cases have katatonic symptoms in common.

Post-Rolandic group (b). 1149 and 1317, as well as 1294 (discussed with the pre-Rolandic cases), belong to an occipital group.

1149 was briefly mentioned in the frontal connection above, because the prominence of the frontal region (which could not be differentiated on palpation from the remainder of the sclerotic brain) was emphasized by a local frontal leptomeningitis. In point of fact the occipital regions were more markedly sclerotic than the rest of the brain. The case might be asserted to present a beautiful instance of anatomoclinical correlation, were we to insist on the relation between the occipital gliosis and the well-defined, constantly recurring, voluntarily executed visual episodes ("communications with God"). Obviously, such a superfine correlation would mean running a good horse too hard. Those "communications" must have involved numerous cortical events outside the occipital region. It seems safe to maintain, however, that, granting some agency exerting a mildly destructive or irritative effect upon the occipital region, a useless mental habit like these "communications" would probably assume a visual coloring. The existence of disease in a given brain-region may well be conceived to determine the course of events in the intact remainder. The histological examination of this case is incomplete, but I conclude from available sections that the calcarine cortex-type is relatively intact, whereas the common occipital cortex-type exhibits much more marked gliosis and satellitosis. In this early phase of our problem, it seems best to rely upon coarse and well-defined qualitative distinctions rather than the cell-enumerations which later work will demand. I judge from recent comments on cortex-architecture that the occipitocalcarine relations will be the most vulnerable point of attack in this direction.

1294, which has been discussed above, also exhibited similar histologically demonstrable variations in the intensity of lesions in the calcarine and occipital regions (common occipital type more markedly affected in the infrastellate layers). As a matter of fact, however, in 1294 the hallucinations shown were auditory rather than visual (though the patient once broke glass to reach her husband being crucified). The brain showed frontal, cerebellar, and pontine gliosis, in addition to the occipital. No temporal gliosis was made out macroscopically, but there were foci of leptomeningitis, both at temporal and at frontal tips.

1317 again breaks down in anatomoclinical correlation much as does 1294, since, despite the occipital microgyria, the hallucinations, so far as was made out clinically, were auditory. There were some religious delusions.

With respect to relative developments of paranoidal and katatonic features in this occipital sub-group, it has been pointed out that 1149 was a classical paranoid case with a few katatonic symptoms toward the close of life (32 years' duration). 1317 was more doubtful but probably can be interpreted as mainly paranoidal; katatonic symptoms developed late in a course of 21 years. 1294 was paranoidal.

If we compare the sensory-perceptual group (a) cases 1137, 1168, 1298 and 1310 with the occipital group (b) 1149, 1317 (1294), we cannot but be struck with the predominantly katatonic character of group (a). The physiological correlations between katatonic symptoms and the sensory-perceptual field are briefly mentioned in Chapter V.

Infra-Sylvian Group.

I have provisionally placed but one case, 1319, in this group, a paranoidal case, probably upon an imbecilic basis. There are no striking anatomoclinical correlations in the case. This group will undoubtedly grow with further experience. 1294, *e. g.*, showed focal leptomeningitis of the temporal tips.

Cerebellar Group.

It is noteworthy that the cases which we procure at autopsy in dementia præcox are provided as a rule with multiple lesions. This is particularly true in the advanced cases, where interpretation may be difficult by reason of the fact that gliosis has overtaken the brain as a whole. This difficulty reappears in the cerebellar cases.

1034, however, is a macroscopically pure case of sclerosis of the dentate nuclei of the cerebellum. Clinically 1034 was a classical example of *cerea flexibilitas,* in an Italian of 35 years, who began with paranoid symptoms (feared anarchists), and in less than six weeks became typically katatonic. Microscopic examination shows in various areas of the brain a gliosis which had escaped palpation in the gross. Some of the areas of intracortical alteration were undoubtedly far too small to attract attention macroscopically. There was a slight satellitosis of the frontal region. The case appeared then, like many other cases of this series, microscopically not so definite as the data of palpation had indicated.

1168 is a case which has been briefly mentioned in the sensory-perceptual sub-group of the post-Rolandic cases as showing a hypoplasia of both postcentral gyri in their upper two-thirds. In addition thereto there was a sclerosis of the olives, of the right dentate nucleus of the cerebellum, and of the cacuminal and clival portions of the cerebellum. This case was classified as hebephrenic, but mutism, resistivism, assumption of fixed attitudes and impulsive rocking movements give rise to the suspicion that katatonic features cannot be excluded. A congenital element is also very possible from both history and brain findings.

A third case, 1143, showing almost the same findings in the brain has been excluded from the group of typical dementia præcox cases but might be included upon a more liberal interpretation of symptoms.

Other cases would have to be added to this group on the score of serious microscopic alterations, which were made out in the face of protocols to the effect that the cerebella were macroscopically normal. The group is, therefore, actually much larger than the two cases (1034 and 1168) would indicate.

Provisional Grouping of 14 Cases without Recorded Gross Lesions.

I have analyzed in some detail the cases with recorded minor gross lesions and anomalies to the number of 15. There are 14 outstanding cases having a clear clinical title to the diagnosis of dementia præcox, but in which no gross lesions were recorded. It is of interest to learn what light a microscopic examination will throw upon these cases and whether any cases are subject to a tentative topographic grouping.

There are several cases about which there is no doubt that they actually belong in the gross lesion group. Thus 1145 should, perhaps have been excluded altogether from this study since the protocols were mislaid. Ample block material exists, however, which microscopically shows characteristic satellitosis of the deep cortex-layers and a marked gliosis of the dentate nuclei (more marked left than right). This case might well be placed in Table XVII above, as well as in the cerebellar group.

1145. 10705. F. 37. paranoid. 6y. Brain wt. 1185.
(Pregnancy at origin.)

I am sure also that with increasing experience, case 1036 would have become an accession to the gross list in the cerebellar group. A sketch of this case was presented by the writer in 1907 in his study of the granule layer of the cerebellum.[23] 1036, 11317, M. 28, hebephrenic, 6y; cardiorenal, renal 6+y; brain 1175g.

778, a paranoid case upon an imbecilic basis, I should desire to place (with some trepidation) in the superior frontal group. The reason for this is that the superior frontal gyri, far more than other regions examined, gave evidence of a sclerotic process: considerable gliosis of the underlying white matter, superficial gliosis of rather focal character, and perhaps a slight generalized gliosis of the whole gyri, with infrastellate satellitosis. That the process was not confined to this region is true, and neuroglia cell mitosis was a curious finding in the right precentral gyrus. The paranoid features had come on two years before death at 41 in this imbecile. Very possibly the case scarcely belongs with dementia præcox as usually conceived; but it seems certain that a similar process has begun in the tissues.

1081, a suicide, can with some confidence be placed in the postcentral sub-group, if only by the evidence of the stained sections which demonstrate a marked inequality in the two postcentral gyri. After considerable search, a focus of gliosis and satellitosis was found in one of the orbital regions. This case, a good instance of a hebephrenic with onset at 18 and suicide at 45, shows how a minor lesion—anomaly or acquired lesion, it would not be safe to say which—can be overlooked at autopsy. Had not the postcentral gyri been sectioned in coordinate places and had not the orbital gyri been sectioned, this brain might well have passed into the "normal" group both macroscopically and microscopically.

1208 is a case described by Ayer and the writer in 1908,[24] in which the gross findings are so altered by the effects of a suicidal attempt and by terminal metastatic brain abscesses that a judgment concerning essential lesions of dementia præcox is difficult. The case should perhaps be excluded from the whole series on the ground of complications.

So excluding 1208, we arrive at the judgment that 15 cases in which gross lesions were actually described, together with four cases in which (in all conscience and with greater experience) gross lesions *should* have been observed, our total of gross lesion cases would run to 19 in 28 (the chosen uncomplicated 29 cases minus case 1208). This result would mean that gross lesions—focal atrophies and aplasias, and a few focal and diffuse glioses without visible atrophy—are found in 68 per cent of a series of typical dementia præcox cases, from which have purposely been previously excluded all instances of frank arteriosclerotic and coarsely wasting processes.

It seems strange that such a high percentage of visible and tangible lesions should have escaped attention, if this Danvers series is at all typical of dementia præcox in general. I am sure that in many laboratories the brains of autopsied cases fail to get intensive study until after long immersion in formaldehyde solution, which obliterates (or by distortion perhaps conceals) minor size-differences in gyri. Moreover, anatomists, familiar with sculpture anomalies of such relatively plastic organs as the liver, kidney and spleen, are inclined to dismiss cerebral anomalies of sculpture as of the same minor order of interest. Again, the careful palpation of the cerebrum and of the cerebellum is not duly practiced in all laboratories, nor are blocks for microscopic examination chosen on the basis of such intensive inspection and palpation of the brain as careful work demands.

Our own experience has shown how difficult it may be to keep one's house in order for intensive work. Eight cases are outstanding in which notes of gross lesions are missing. Of these eight, four show in certain regions characteristic gliosis and satellitosis (891, 944, 977, 1165). The other four (794, 806, 873, 1006) have so far proved refractory to our efforts to show stratigraphic alterations.

The result is that 24 out of the chosen 28 cases show either gross and microscopic lesions or microscopic lesions alone, *i. e.*, 86 per cent.

V. The Topographic Idea in the Study of Dementia Præcox and Allied Conditions.

The eternal hope of the neuropathologist is the hope of showing visible "changes" in the nervous system in the functional psychoses, and not only *in* them but *of* them. All insanity, we hear on every hand, is really nothing but brain disease, and, if our technique were only better, we should be able to point out the particular brain-changes which are responsible for insanity. I was assured by an enthusiastic psychopathologist that these brain-changes are actually so certain to exist that we should not waste our time looking for them.

There are reasons which make this equation:

$$\text{Insanity} = \text{brain-disease}$$

really erroneous. In the first place, certain psychiatrists to the contrary notwithstanding, modern work has shown that the equation should better read

Insanities = brain-diseases,

and in the particular form

Some insanities = brain-diseases

perhaps we should be inclined to accept at least the spirit of the statement.

Ever since the doctrines of Flourens were overthrown, from the days of Hughlings Jackson and Hitzig down to the era of the topographers (Campbell and Brodmann, for example), it has been known that the brain is a complex of organs. The brain has parts. Yet those authors who assert that insanities are diseases of the brain are as a rule quite silent as to the brain-*parts* involved. The brain as an organ of mental disease is for these authors really the old Flourens brain, having interchangeable parts like a liver or a kidney.

The only justification for this view of which I am aware is the sound idea that the brain, although its parts are not homogeneous and interchangeable, still works in a certain integrated, organized way, and, when disorder and disorganized workings of brain-elements supervene, then mental diseases appear. Thus Wernicke supposes that

insanity = disease of the association elements of the brain.

This is a definite advance upon older conceptions, at all events in clearness. I suppose no one doubts the conceivableness of a mental disease based upon such transcortical lesions of association fibers as Wernicke supposes. But few would be so bold as to generalize the transcortical-injury idea[25] to cover the great bulk of mental diseases.

Even in the field of aphasia, one observes with recent writers a tendency to replace the focal-destruction theory with some theory more consonant with modern ideas as to the tremendous breadth, and complexity of the cortical areas subtending speech. From the psychological and logical side comes a vigorous plea from Wundt[26] against the fashionable focalizing of the speech functions in specified areas.

Thus a curious situation develops. On the one hand, the topographers, both physiological and histological, are demonstrating more and more the extreme delicacy of subdivision which exists in the brain-cortex, as elsewhere in the nervous system, so that one gains the idea that perhaps no parts of the brain are functionally interchangeable, save by re-education. On the other hand, logicians and critical workers are calling a halt upon the focalizers and denying some of the most classical and approved localizations. These latter objections are brought with the more force against the localization of a complex function like speech, which savors of the old faculty-psychology and contains a *soupçon* of phrenology.

I believe we should be even more critical concerning the structural foundations of mental disease. Suppose we grant that any mental symptoms you please, *e. g.*, delusions, hallucinations, negativism, *cerea flexibilitas,* have a cerebral origin, is it necessary to suppose likewise a cerebral disease, as a basis therefor? Yes, some would reply, a cerebral disease, but not necessarily structural, perhaps functional only. Even the latter escape I should be tempted to forbid.

Consider diabetes mellitus. The glycosuria has in one sense a renal origin. But it would be a mistake to consider diabetes mellitus a renal disease, structural or functional. I believe that the brain permits certain mental symptoms to develop and purveys these symptoms, much as the kidney of a diabetic permits and purveys glycosuria.

Similar considerations hold with respect to the purveying of convulsions by the brain, an account of which I presented in a paper on the mechanism of gliosis in epilepsy. Neither a convulsion nor a katatonic impulsive movement nor the clenched fist of a thug is adequately explained by lesions of the muscles involved, by lesions of the motor nerves or spinal cord, by activities in the precentral gyrus, or even necessarily by any post-Rolandic or pre-Rolandic brain mechanism or combination of mechanisms. Perhaps, indeed, the reason lodges back of the central nervous system: the convulsion might have been a phenomenon of reflex epilepsy due to intestinal worms, even the katatonic movement might conceivably prove a normal and proper reaction to some received stimulus, and the thug's brain might have been quite "normal" while engaged in permitting asocial acts for whose source one should seek far afield.

On such grounds it has not seemed certain to me that mental disease is necessarily brain disease or that, were we able to inspect thoroughly all brain-parts, we should necessarily discover "changes" therein in mental disease. Perhaps the thyroid or the pituitary glands might induce mental symptoms without inducing brain "changes," over and above the proper physiological changes going on in any brain-part during the execution of its normal function. We might be forced to look into the thyroid for the cause of some mental diseases, just as into the pancreas for that of a diabetes mellitus.

A priori, therefore, it has not seemed to me at all necessary that diseases like manic-depressive insanity or dementia præcox (to use Kraepelin's nomenclature) should exhibit, even theoretically, brain-changes. One was especially disposed not to conceive brain-changes of a universal character, such as the universal liver changes in phosphorus poisoning, as underlying these diseases. No doubt there are instances of such universal brain-change and no doubt mental symptoms occur as a consequence. Hyperpyrexia might serve as an example. General paresis, however, our paradigm in this field, despite the severe and widespread brain changes which characterize it, is still an example of a disease of focal character. From its protean and progressive character, a theoretically similar focality for brain lesions in dementia præcox was thought probable. The mild, irritative and persistently complex character of many symptoms in dementia præcox seemed to argue very mildly destructive or irritative lesions, such that an occasional definite cure or disappearance of a given symptom or set of symptoms could be effected by removal of irritating factors or by advancing destruction of the offending elements.

If these contentions were sound, it became clear that no random block of brain tissue could demonstrate the nature of dementia præcox, as a particular block of lung tissue might demonstrate that of pneumonia. Neither would all the cells be equally or peculiarly affected nor would the cells of certain strata do more than demonstrate the effects of disease in those strata.

But, if the cells or strata of no random block of brain tissue could serve as a test of dementia præcox, would not particular and happily chosen blocks, or even ideally possible total-brain sections suitable for cytopathology, solve the problem. I suppose all would agree that such work might solve the problems at least of localization and possibly of pathogenesis in dementia præcox, provided that the disease is really a brain disease.

I therefore began to study all cases of dementia præcox accessible to me (the protocols and prepared sections from the Danvers collection made in Prof. Barrett's service and my own), to get a general view of the subject. As will be seen, I at first included with type cases also cases only doubtfully belonging in dementia præcox, and these I have excluded from the conclusions of this report, although many exhibited lesions which might well serve, if we were surer of our conditions, to bring the cases back into the group.

The histopathology, although studied in connection with many of the lesions, has been left in the background to avoid involvement in a tangle of discussion concerning intracortical reflex-arcs.

Conclusions.

1. Existent evidence for the organic nature of dementia præcox is not wholly convincing, since (a) the cytological changes described are found also in cases of toxic deliria and in cases complicated by severe visceral disease, and (b) the stratigraphic changes described are found also in certain senile cases without characteristic symptoms of dementia præcox.

2. Resort must, therefore, be had to the topographic idea, for the adequate exploitation of which total-brain sections, with cytological exploration of *all* areas, are ideally necessary.

3. Random blocks of brain tissue with demonstration of satellitosis, infrastellate gliosis, or disintegration products of cell disorder will throw little light on the mechanism of dementia præcox.

4. The data of the functionalists (dissociation, sejunction, intrapsychic ataxia, and the like) are of the utmost importance as indicating the essential focality of the pathogenic process and the focal variations in its severity.

5. The curability of certain cases, the remissive character of some cases, the speedy disappearance of particular symptoms, the persistent complexity of reaction in some instances, the absence of characteristic severe projection-system symptoms, all indicate

that the process is histopathologically mild and that the focal changes found will be but slightly destructive or even irritative (in the sense of slight injuries readily repaired or compensated for).

6. Grossly destructive lesions of a transcortical character in Wernicke's sense might conceivably effect, *e. g.*, a permanent katatonic complex and doubtless will be found to do so occasionally; but the protean and progressive character of dementia præcox will exclude such transcortical injuries from playing a large part in the pathogenesis.

7. The focal lesions to be sought for will doubtless escape macroscopic notice in many instances, since the volume of apparatus engaged in effecting very prominent symptoms is often slight and spread very thin in numerous areas.

8. Studies of the "soft brain" and of gliosis in epilepsy have proved, however, that even comparatively slight degrees of cortical gliosis can often be palpated at autopsy.

9. Palpable glioses of a focal or variable character, combined in numerous instances with visible atrophy and microgyria, have been found in over half the series under examination, in cases regarded as clinically above reproach and *not* subject to coarse wasting processes, focal encephalomalacia, cortical arteriosclerosis, or diffuse chronic pial changes.

10. The frequent co-existence of several foci of sclerosis or atrophy in the same brain and the microscopic observation of milder degrees of nerve-cell disorder and gliosis in regions without gross lesions tend to the conception that the agent is more general and diffuse in its action than would seem at first sight, so that future research may well demonstrate that certain instances of coarse brain wasting and even of diffuse chronic leptomeningitis belong in the group (microscopic corroboration necessary for assigning values to focal variations).

11. The microscopic examination of the residue of cases in which gross lesions or anomalies were not described shows the same tendency to gliosis and satellitosis in numerous instances and the same tendency to focal variations from gyrus to gyrus exhibited by the gross lesion group. These findings suggest that the minor gross lesions and anomalies of several cases actually escaped notice (the protocols, though drawn up with a certain

system, are by various hands) at autopsy, so that the probable actual proportion of gross lesions is 68 per cent. If microscopic evidence is resorted to, the "organic" proportion in our series rises to 86 per cent.

12. Several groups of cases were classified from the distribution of macroscopic lesions, although the focal purity of these cases can often be brought in question from the results of microscopic examination (infrastellate gliosis and satellitosis also in macroscopically "normal" areas).

I. Pre-Rolandic group, including a superior frontal-prefrontal sub-group of paranoidal trend (*cf., e. g.,* case 1062).

II. Post-Rolandic group, including (a) postcentral-superior-parietal (sensory-perceptual) sub-group in which katatonic features are the common factors (*cf., e. g.,* case 1298); (b) occipital sub-group (*cf.* case 1149).

III. Infra-sylvian group (too small for clinical correlations).

IV. Cerebellar group (katatonic features).

13. If these data find general confirmation, they will doubtless go far to unify discussion, since mild, variable and progressive intracortical lesions, proceeding at different rates in different parts of the apparatus, and having the peculiar distributions indicated above, would explain adequately some of the contentions of the dissociationists, while remaining not wholly inconsistent with Kraepelinian ideas.

14. The frontal-paranoid correlation is in line with modern physiological ideas, but it must be granted that the occipital and temporal regions, as elaborating important long-distance impulses, may well play a part also in paranoid states.

15. The cerebellar-katatonic correlation is doubtless in line with some contentions of the Wernicke school, and obvious comments might be made in conection with the proprioceptive functions of the cerebellum (Sherrington).

16. The postcentral-superior-parietal relations to katatonic symptoms are perhaps theoretically the most novel suggestion from the work, but here again the results are not inconsistent with modern physiology.

17. The topographic study of dementia præcox brains, both gross and microscopic, is commended as likely to shed new light on the pathogenesis of certain symptoms, notably paranoidal and katatonic symptoms.

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XXVI

REPORT ON THE MENTALITY OF A SUBJECT FASTING AT THE NUTRITION LABORATORY OF THE CARNEGIE INSTITUTION OF WASHINGTON, BOSTON, MASS., FROM APRIL 14 TO MAY 15, 1912.

BY E. E. SOUTHARD, M. D.

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THE MENTALITY OF THE FASTING SUBJECT FROM THE PSYCHIATRIC POINT OF VIEW.

By E. E. Southard, M. D.

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The subject presented no signs or symptoms of (*a*) insanity in the sense of a mental disease of legal significance. The question might arise whether he did not belong in the wider circle of so-called (*b*) psychopathic personalities. Many alienists might feel that any professional faster would potentially belong in such a group of psychopaths, despite the fact that they might well be demonstrably not insane in a legal sense. Another possibility is that, although the subject might not be legally insane or in any sense psychopathic, yet he might possess (*c*) an abnormal personality. Doubtless the group of abnormal personalities, including various geniuses, is a still broader circle of conditions, including within it the psychopathic personalities within which again the legal insanities fall.

The general impression conveyed by this subject was that of a personality abnormal, in the sense of the term "unusual." There is doubt whether he should be called in any important sense psychopathic, although some alienists would undoubtedly tend to class him as such.

The psychological tests carried out *in extenso* by Dr. Langfeld showed no important disorder of perceptual processes, nor was there at any time any unclearness of consciousness or reduction or perversion of ideation or attention. There were at times traces of an abnormal or unusual fixation of attention, and there was some increased vividness of interest in various phenomena. There was no abnormal ductility of the attention, except in the direction of matters intimately concerning the patient's ego, such as proofs of mental normality, proofs of previous accomplishment, and (above all) proofs of essentially scientific interest on the part of the subject in the fasting experiment.

On the side of perception, therefore, the only traces of disorder of which there is evidence are suggestions of increased vivacity during discussion of egocentric matters. This symptom, when pronounced, is observed in the disease named by Kraepelin "manic-depressive insanity," especially in the maniacal phases of the disease; but inasmuch as during the interviews (which largely preceded the tests) there was no sign of a heightened receptivity for external impressions or any behavior which could be interpreted as amounting to an increase of attention involving general matters outside the ego, I am compelled to conclude that there was really no evidence worth considering of morbid disorder of the attention.

Upon the intellectual side no evidence of disorder of memory or of temporal and spatial orientation or disorder in ideation and conception, or disorder in the train of thought or in imagination, could be demonstrated. So far as observed, the patient's conversation betrayed no mannerisms in speech or sound associations indicating unusual habits in detail of thinking. As to the faculty of judgment and the drawing of conclusions, the nature of the subject's situation might tend to prejudice one in favor of thinking that we might be dealing here with a disturbance of judgment which could lead to delusion formation and potentially to paranoia. Of course there is, theoretically, doubt as to the nature of paranoia; but many authorities are inclined to think that paranoia always develops upon an emotional basis. It was not possible to discover any adequate emotional basis for the tendency to exaggerated egoism which the subject undoubtedly at times tended to show. The naïve account of this egoism would be to regard it as due to a natural desire to "shine" in society—a desire to be "different" marking the so-called eccentric person. There are modern theories which go so far as to regard this egoism as a form of psychic exhibitionism which may even have deep-lying sexual bases (reference is here made to doctrines of so-called Freudians), but of this in the present case there is no evidence. Aside from the theoretical uncertainty of this description of egoism, there was no evidence of either an abnormal interest in sexuality by the subject, or of hesitations or unusual expressions in the midst of conversation on such topics, suggesting an abnormal emotional center of this type. However, the patient had what we are accustomed to term a somewhat Oriental view of society, and it is possible that a more skillful observer or a more protracted observation could have discovered some materials for a Freudian explanation of the subject.

The patient beyond question believed himself of greater importance in the world, and especially of greater scientific importance, than the facts might warrant. He believed himself in many respects essentially superior to other fasters. Of course an attitude like that of this subject has been known to be transformed into an overt paraphrenia systematica, to use Kraepelin's designation for certain paranoidal conditions in the third volume of his eighth edition, 1913; there was at the time of examination no sign of such transformation.

A consideration of the emotional and volitional sides of the subject can hardly be fair to the subject or observer on the basis of the interviews held, and conclusions should rather be drawn from whatever data Dr. Langfeld may have obtained than from observations of the writer. There remains doubt whether the eccentric abnormality of the individual is of intellectual or emotional origin. Perhaps it would do no violence to present theory to state that it is a mixture of the two.

In brief, therefore, (1) there are no evidences of committable insanity in the subject; (2) some alienists might think the subject a psychopathic personality, but (3) the subject is probably an eccentric and not a psychopathic person. There are certain traces of psychic exhibitionism in the case. No erotic origin for this phenomenon was discovered, and it may better be taken on a more naïve basis as an exaggeration of a frequent phenomenon. The egoism was rather of a childish character. All signs pointed rather to vanity than to ambition. The subject belongs to a group of reformers and self-constituted saviours, and the ultimate decision as to his character must depend upon developments of psychiatric theory as to the intellectual, emotional, and volitional significance of such reform tendencies. The odds at present favor an emotional basis for these tendencies.

XCVI

28

XXVII

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THE SIGNIFICANCE OF A HOMEOPATHIC FOUNDATION FOR CLINICAL RESEARCH AND PREVENTIVE MEDICINE.*

BY E. E. SOUTHARD, M.D.,

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Clinical research and preventive medicine — I have tried to conceive how these terms would have sounded to Hahnemann a century ago. The idea of clinical research would not have been quite foreign to him. The necessity of testing or "proving" drugs by their effects on healthy individuals was, indeed, always urged by Hahnemann. The idea of preventive medicine, born of modern bacteriology, would hardly have been understood in Hahnemann's day. Yet, could he have followed the progress of modern work in immunity, he might well have claimed a kinship between the principle of *similia similibus curantur* and certain principles of immunity. And he might well have been astonished at the remarkable effects of sensitization with extremely minute doses of certain substances in the phenomenon known as anaphylaxis.

Similia similibus curantur! How curious a coincidence it is that in the same year, 1796, that the German Hahnemann, of Meissen, proclaimed the principle of homeopathy, the first actual experiments toward the principle of vaccination for smallpox were being made by the Englishman Jenner, on the farms of Gloucestershire. Of course neither Jenner nor Hahnemann could claim absolute novelty for his ideas. The introduction of inoculation for smallpox into England was made by Lady Montagu in 1721, and the principle of *similia*, etc., had assumed a fairly definite shape in the sixteenth century with Paracelsus, the alchemist of Switzerland.

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* Delivered at the dedication of the Robert Dawson Evans Memorial Building, March 6, 1912.

How much the national environments of Jenner and Hahnemann came to influence their products may never be said. Hahnemann lived in the age of the *Naturphilosophie;* the year after Hahnemann's announcement appeared the "*Wissenschaftslehre*" of Fichte and the "*Ideen zu eine Philosophie der Natur*" of Schelling. The scientific victory over the *Naturphilosophie,* and over the more elaborate and much misunderstood doctrines of Hegel, came for Germany in the late twenties and the thirties of the nineteenth century. In the days of Hahnemann's development, there was little or no *exakte Wissenschaft* in the German universities: any one with new ideas had almost perforce to cast them into a system to attain a hearing. No concrete work like Jenner's was then being done in Germany, or, for that matter, in France, if we except the "*Recherches physiologiques*" and "*Anatomie générale*" of Bichat (1800–1801). The epoch-making work of Laplace ("*Exposition du système du monde*") appeared in the very year of Hahnemann's announcement. In 1798 came Cuvier's "*Tableau élémentaire d'histoire naturelle,*" followed soon by the "*Lecons d'anatomie comparée*" (1800–5).

Hahemann's "*Organon*" appeared in 1810. It was the same year that John Dalton's "New System of Chemical Philosophy," embodying the atomic theory, was printed. It was the year after Lamarck's evolutionary ideas were published ("*Philosophie zoölogique,*" 1809) and the year before Charles Bell proclaimed what was to be the greatest English discovery in physiology since Harvey, — the difference between sensory and motor nerves. What chance of recognition did the literary-sounding *similia*, etc., have beside the atomic theory, the idea of adaptation, the inner mechanisms of the nervous system? And when Hahnemann did venture into concrete statements concerning causes with his *psora, syphilis* and *sycosis,* he was singularly unfortunate. But neither the trinity of *itch, great pox,* and *fig-warts* nor the singular dosage system — a later creation of Hahnemann — can be considered, as I understand it, an integral portion of the Hahnemannian doctrine, which stands or falls mainly on the doctrine of *similia,* etc., which has given it its name.

A fair example of old-fashioned German system-making, homeopathy has never obtained large recognition in the new Germany or at any time in individualistic England, but it did obtain considerable foothold in France, where clarity and definiteness of form have always appealed. It was to France that Hahnemann eventually repaired, and there he was buried with due honors in Père-Lachaise.

In the very year that the philosopher Hegel died and the physiologist Johannes Müller was demonstrating the truth of Charles Bell's doctrine of the nerves, homeopathy was virtually read out of Germany (1831). In America, the land of contrasts, homeopathy has flourished more than elsewhere and is virtually a religion with some. Almost with *Schadenfreude,* the opponents of homeopathy have watched it, like various religions, develop inner dissensions. High potency purists and low potency innovators are found. Some claim the virtues of the rest of medicine plus those of homeopathy!

Committed to a system, what were homeopathists to do? They could not sit by and watch the procession of new ideas. As science developed, the doctrines of immunity seemed a living and concrete instance of *similia*, etc. Syphilis certainly has vindicated the interest of Hahnemann therein, if psora and sycosis have not. The new ideas of radio-activity, certainly not homeopathic in their origin, could be claimed as demonstrating a certain potency of unimaginably small things, not to say a spiritual agency such as some homeopathists invoke.

Here in Boston, perhaps the leading center of homeopathy in the world, we have learned respect for homeopathists. Personally I have the greatest respect for homeopathists, but no more for homeopathy than for many other systems helpful in their day, but now inadequate. The river of homeopathy has had a century or so of separate flow round an island of prejudice. But that island had more length than breadth, and now the river itself seems about to flow once more into the deep irresistible main river of general medical progress.

A concrete example of this I see in my work as pathologist to the State Board of Insanity. This board has to supervise the homeopathic institution of our commonwealth at Westboro. In my annual reports I find much to commend publicly in the Westboro work, and particularly the work of Dr. S. C. Fuller, pathologist at Westboro. No better enthusiasm prevails than that found in Fuller's laboratory. His spirit and that of Dr. W. H. Watters show that the new building means no new conception to Massachusetts homeopathists.

Now that the Robert Dawson Evans Memorial Building has been dedicated to the interests of clinical research and preventive medicine, let us, therefore, take it as a sign that the Hahnemannian system, like most systems of this world, will prove self-destructive, but at the same time productive of a new self the better for the existence of the old. I understand that the higher textual criticism has been applied to homeopathy also by the true believers, and that *similia similibus curantur* is a phrase not found in Hahnemann. Instead, we find only the subjunctive *curentur.* Most human designs are in the subjunctive. If the workers in the new Memorial Building admit no universal affirmatives and stick to the *lets, mays* and *ifs* of science, perhaps old Hahnemann himself from his spiritual state of infinite trituration will beam down upon us all in a refinement of unexpected joy.

XXVIII

PSYCHOPATHOLOGY AND NEUROPATHOLOGY: THE PROBLEMS OF TEACHING AND RESEARCH CONTRASTED *

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The ideas that I wish to bring to this symposium are few, and I hope not too unorthodox. How shall research psychology and research medicine come together, on what ground, and to what ends? I wish (1) to insist strongly on the unique value of the pathologic method, not merely for the diagnostic and therapeutic purposes of medicine, but for biology as a whole and for the most vital of biologic sciences, psychology. I wish (2) to point out how pernicious in research may be the dogmatic insistence on the doctrine of psychophysical parallelism in medical or premedical courses in psychology—pernicious because it inhibits the free interchange of structural and functional concepts and the passage to and fro of workers in the several sciences. I wish (3) to show that psychology and physiology have more in common than either has with such structural sciences as anatomy and histology, and that the main common element of both mental and cerebral processes is the time-element as against the space-element of the structural sciences. On this ground (4) I conceive that the mind-twist and brain-spot hypotheses for the explanation of certain forms of mental disease are entirely consistent with each other, since from a different angle each is dealing with the same facts. Above all (5), let us not divide up the tasks of research as we divide up the tasks of teaching, since research, looking to the future, defies the compartments of the past.

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* Read in a symposium on "The Relations of Psychology and Medical Education" before a joint session of the American Psychological Association and the Southern Society for Philosophy and Psychology, held at the Government Hospital for the Insane, Washington, D. C., Dec. 28, 1911.

> "It always leads to a better understanding of a thing's significance," wrote W. James, "to consider its exaggerations and perversions, its equivalents and substitutes and nearest relatives elsewhere. . . . Insane conditions have this advantage, that they isolate special factors of the mental life. . . . The study of hallucinations has in this way been for psychologists the key to their comprehension of normal sensation, that of illusions has been the key to the right comprehension of perception. Morbid impulses and imperative conceptions, 'fixed ideas,' so-called, have thrown a flood of light on the psychology of the normal will; and obsessions and delusions have performed the same service for that of the normal faculty of belief."[1]

It is perhaps in such complex fields as this that the natural analyses effected by disease possess their widest scope. Even where more artificial analysis is possible, the pathologic method has often yielded the most fortunate short cuts. One of the richest generalizations of biology at large (the dictum *omnis cellula e cellula*) could hardly have been achieved without decades of labor by a commission of biologists empowered to study normal cells, and only normal cells. The utilization of abnormal material gave a long-range induction almost at once. The pathologic foundation of the doctrine of evolution is obvious to anyone who considers what survival of the fit means in terms of the unfit. The doctrines of immunity derive an indispensable constituent from the law of regeneration in surplus, which Weigert observed in his studies of interstitial tissue. The bacteriology of disease has afforded some of the shortest cuts and the longest new ranges of thought of which we know or can conceive. The more complex the subject of our study, the less progress do we make by confining our attention to the normal presentment of that object. Normality is baffling, like the roc's egg to the climbing Sinbad. A niche, a wedge, fragmentation, dissection, division of intellectual labor, all the screening and sifting which lie at the basis of experimentation, these characterize the method of pathology, which pays small heed to the pedagogic divisions of any former stage of a given science. The research pathologist follows the trail of the concrete through whatever ranges of the abstract become necessary, and through no others.

It is here that the school divisions of psychology and brain physiology, of psychology and brain anatomy, of brain physiology and brain anatomy, of anthropology and social statistics, of sociology and criminal anthropology, and a host of other abstract school divisions have entered to divert the research worker from his duty to the concrete complexity.

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[1] James, W.: Varieties of Religious Experience.

Particularly dangerous I find to be certain school tendencies born of the doctrine of psychophysical parallelism. The teacher of psychology desires to keep *mind* logically distinct from *body;* the teacher of physiology disclaims expert knowledge of psychology; the teacher of brain anatomy almost skilfully avoids giving his point of view about anything remotely functional.

The student grows to a feeling that the confines and septa of pedagogy are the confines and septa of research. For the development of psychopathology and of neuropathology, which I consider to be school divisions of knowledge of no ultimate logical importance, no other single doctrine has, to my thinking, been so pernicious as the doctrine which proposes to separate mind and body before we know much about either.

Most of us remember James' neat criticism of the *ohne Phosphor, kein Gedanke* psychology. "The phosphorus-philosophers," said James, "have often compared thought to a secretion. 'The brain secretes thought as the kidneys urine, or as the liver secretes bile,' are phrases which one sometimes hears. The lame analogy need hardly be pointed out. . . . We know of nothing connected with liver- and kidney-activity which can be in the remotest degree compared with the stream of thought that accompanies the brain's material secretions."

I remember smiling as a college student at the folly of these phosphorus men, thus dispatched at a blow. The fact is, a friend explained to me, *ohne Gedanke, kein Phosphor.* Thereafter I was not long in succumbing to the artistic simplicity of idealism.

It took me many years to learn that neither phosphorus, etc., nor the streams of thought could be dealt with so simply.

The proportions:

Brain : Thought : : Liver : Bile

or

Brain : Thought : : Kidney : Urine

are obviously fallacious; but, if we alter the proportions slightly to

Brain : Process of Thinking : : Liver : Process
of Secreting

and

Brain : Process of Thinking : : Kidney : Process
of Excreting

we have destroyed the fallacy which James ridicules.

We find that liver- and kidney-activity have one important thing in common with the stream of thought — namely, activity itself, the temporal features of all processes whatever.

One more interactionist! I hear you say. No, I reply, that would hardly be fair. How can we prattle interaction, if we do not know the factors we declare to interact? These factors in the interaction-complex, I repeat, we simply do not adequately know either in the concrete or in the abstract.

If not a parallelist and not an interactionist, what remains for a student? Must he not relapse into crusty mere critique or cowardly agnosticism?

Some years ago I ventured from my chosen path of brain analysis in mental disease at large to a discussion of dementia præcox in particular. I found that practically everybody had taken sides. It had become a game. The hypothesis of psychic factors was strictly opposed to the hypothesis of encephalic factors. Tangles and twists in the mind appealed to some; blots and spots in the brain appealed to others.

Contrary to my presuppositions (I do not pretend to be exempt from presuppositions), I found in the brains of subjects suffering from something like dementia præcox, certain lesions, partly congenital anomalies, partly lesions acquired in the individual's life. I was led for the moment, and still feel the impulsion, to confide in the brain-spot hypothesis *for dementia præcox.*

Then the secret is out! The reader believes that there are compartments in mental disease such that mind-twists work here, brain-spots there? No, I reply, I am not so naive as that, nor are the facts so simple.

"They quote you," said a practical psychotherapeutist to me the other day, "to the effect that dementia præcox shows lesions, and is therefore incurable, and is anyhow not subject to my poor psychotherapeutic efforts."

"Who quote me?" said I.

"Why, the materialistic doctors of the clinic!"

This was the sequel of my well-meant endeavor to work on an apical problem! The facts are these: I am not convinced that we can safely entify dementia præcox in the first place. I am not sure that the anomalies and scleroses which I found are primary causes in the group. I am still less of the opinion that the changes are secondary to mental twists. I think the lesions are such as to interfere with proper cerebration, just as water on the knee interferes with proper walking.

"I have no objection to the lesions of dementia præcox, if you do not regard them as primary," wrote one friend to me. Precisely, I reply. The lesions are neither primary nor secondary. They, or the cell-arrangements involved, permit or purvey the symptoms and signs of dementia præcox. The same facts viewed from one aspect are structural, from another aspect functional. Structure is in the main the spatial aspect of facts and events, function in the main the temporal aspect of the same facts and events. To say that mind precedes matter, or matter precedes mind, is to say that time precedes space or space precedes time. If you look sharply at a frozen moment held as a sort of preterite before your eyes, you will hardly discover more than something structural. If you follow the object for a time, you will discern inner or outer changes in the object, qualitative, quantitative, positional, or relative, which entitle you to describe the object only in functional terms.

Brain-changes and mind-changes have at least this temporal aspect in common: Whether both types of change are concretely identical is for research to decide. Pedagogy, the logic of the past, can decide nothing of the sort. Both types of change in virtue of being changes *überhaupt,* are opposed to the structural, *ex hypothesi* unchanging, killed, fixed and mordanted objects which neurology describes.

Suppose then that *for teaching purposes* we keep structure and function apart; suppose we even go a step farther and, for teaching purposes, separate function into two kinds, cerebral and psychic; I maintain that in research we should let the facts lead us where they will, over the hills and dales of physiology, into the deep borings of anatomy, or upward into the ethereal reaches of psychology. We have already weakened the pedagogic boundaries of many ancient sciences, and by new surveys, protracted litigation, and a thoroughgoing disrespect for precedent *coram factis*, we may achieve shortly new boundaries.

The majority of cases of mental disease are, I am convinced by special studies, characterized by the occurrence of obvious brain-lesions, i. e., even in the present stage of science they possess a structural pathology. Do they therefore possess no functional pathology? Their possession of the two aspects is a truism. Should we not study both aspects?

Furthermore, suppose we learn that, whereas three-quarters of our cases of mental disease exhibit obvious irrecoverable brain-lesions, another quarter fails to show these. Suppose the methods of microscopic research should still fail to show in many cases essential or irreversible brain-lesions, should we not stultify ourselves if we did not abandon *for the research campaign* both that psychopathology which has taught us the main course of our disease and the neuropathology which has proved usefully negative? Should we not repair at once to the chemistry of metabolism, the physiology of internal secretions, and the entire point of view of pharmacology? Discoveries in the latter fields, concrete and pertinent facts, would carry us back to the tissues and back to the processes of the nervous system, to neuropathology, structural and functional, and to psychopathology, and enlighten many dark corners therein. He who adheres to the classical problems as they lie within the teaching divisions of any science is not apt to change the face of that science.

37 Trowbridge Street.

XXIX

MEDICAL CONTRIBUTIONS OF THE STATE BOARD OF INSANITY OF MASSACHUSETTS: INTRODUCTORY NOTE.*

BY E. E. SOUTHARD, M.D., BOSTON,

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ABSTRACT.

Statutes concerning scientific investigation and publication of scientific reports by the State Board of Insanity of Massachusetts (1898).

Maintenance and development of laboratories in the supervised institutions, culminating in the Psychopathic Hospital, Boston, 1912.

Appointment of a Pathologist to the State Board, 1909.

Appropriation for expenses of investigation since 1911.

Fourteen branches of investigation so far pursued.

Summary and Remarks.

FROM the beginning of its work in 1898, the State Board of Insanity of the Commonwealth of Massachusetts has had by statutory law the specific duties of encouraging scientific investigation and of publishing the results of such investigation (Acts of 1898, Chap. 433, Sec. 5); Revised Laws (1902), Chap. 87, Sec. 5; Acts of 1909, Chap. 504, Sec. 6. The latest revision

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* Being S. B. I. Contributions, 1913. 1. *Official information* concerning the State Board of Insanity of Massachusetts is contained in its Annual Reports (Pub. Docs., No. 63) published since 1900. Reports of the pathologist, included therein, began in the eleventh annual report for 1909, published in 1910

(1909) reads that (*a*) "The board shall encourage scientific investigation by the medical staffs of the various institutions under its supervision," and that (*b*) The board "shall publish from time to time bulletins and reports of the scientific and clinical work done therein."

The first of these duties has been faithfully executed in the sense that clinicopathological laboratories have been maintained, improved, and increased in number since 1898. Laboratories with special officers in charge are now maintained at Danvers (1895), Worcester (1895), Taunton (1897), Westborough (1898), Boston (1910), Boston (Psychopathic Hospital) (1912). Special buildings for these laboratories have been provided (Worcester, 1904; Westborough, 1906); and the appropriate modern outfit of laboratories in a psychiatric clinic in the German sense is being gradually installed in the ample laboratories of the Psychopathic Hospital (Boston). It has also happened that the spirit of scientific investigation has not been confined to the special laboratory officers, but has spread to the other members of the staffs and *vice versa*.[1] The mutual reactions between ward and laboratory have often been remarked, and in more than one instance a man trained as pathologist has turned into clinician, and a clinician by training has turned pathologist. The results of the scientific work in these institutions have been published very scatteringly in different medical journals and may be judged by the titles in a bibliography of articles printed which will subsequently appear. Over eighty of these publications have already been listed in a paper entitled "Contributions from the Psychopathic Hospital, Boston, Massachusetts: Introductory Note" and published in the BOSTON

MEDICAL AND SURGICAL JOURNAL, where note has been made of the wide scope of this work, despite its comparative neglect of sociology and psychopathology in favor of neurological and somatological contributions.[2]

As to the second duty above mentioned, viz., that of publication, the State Board of Insanity has hitherto confined itself to concise remarks suitable to its annual reports (Pub. Doc. No. 63) and has with a certain propriety left the business of publication to the institutions specially the source of given investigations. It is undoubtedly wise for the institutions to continue their own publications in the usual form, perhaps with one small feature added, viz., the assigning of an accurate serial number or year number (*e.g.* Contributions from ———— State Hospital, Number ———; or, 1913. 1, 1913. 2, etc.). Such a numbering system is in use or contemplated for the Danvers, Westborough and Worcester contributions, as well as for the Contributions of the Psychopathic Hospital and of the State Board of Insanity about to be issued. The usual form of publication in various appropriate medical or other journals seems preferable to publication in official reports or public documents, first, because the communications thus reach a wider and more suitable audience, and secondly, because the cost of publication is borne rather by the journals than by the commonwealth.

However, in 1909, the State Board of Insanity went a step farther in execution of its duty "to encourage scientific investigation by the medical staffs" by appointing (May 1, 1909) a pathologist, whose duties should consist of (1) supervision of the clinical, pathological and research work in the various institutions under the board's general supervision, (2) visits to the institutions from time to time, and (3) reports to the board. The general problems derived from the pathologist's work in the institutions proved shortly to demand more funds than were readily available in a given institution, and many of the problems were of so general a nature that their extended study could hardly be undertaken in a single institution. Accordingly, there was incorporated in the Acts of 1911, Chap. 688 (the appropriation act of salaries and expenses in the department of the State Board of Insanity) a paragraph appropriating "for the expenses of an investigation as to the nature, causes, results and treatment of mental diseases and defects, and the publication of the results thereof, a sum not exceeding twenty-five hundred dollars." This appropriation has been since continued (1912, 1913). Reports have been printed each year listing the branches of investigation undertaken and briefly describing their results.

Of work having a general scope before the appropriation for expenses was made, the following may be mentioned (see Annual Reports of State Board of Insanity, 1909, 1910):

1. Nature and causes of mental disease beginning between fifty and seventy years of age (Southard and Mitchell). Proof was brought that neither wasting of the brain substance nor damage done by diseased blood vessels is responsible for the mental disease in a good proportion of cases. Alterations in the nerve cells and in the interstitial cells were found, giving rise to the hypothesis of a disorder of cell metabolism in these cases.[3]

2. Nature and causes of senile dementia (Southard). A special group of cases (termed

"senile atrophic dementia") was separated out from the arteriosclerotic and functional cases of mental disease in the aged. Evidences of active and progressive destruction of nerve cells were found in these brain-wasting cases. Attention was called to the fact that in some cases the brain suffers wasting along with all other viscera, but that in some cases the wasting affects the brain and spares the other organs. The causes of the two affections are possibly separate.[4]

3. Errors in the diagnosis of general paresis (Southard). This study was undertaken before the usage of the Wassermann reaction for detection of syphilis and showed an error of 10-15% in the diagnosis. This result has medico-legal importance, and emphasizes the necessity of Wassermann serum and cytological tests which have now greatly reduced the error. The special nature of those cases in which errors were made was described (cerebellar, arteriosclerotic, etc).[5]

4. The margin of error in the diagnosis of mental disease. Ten cases in 250, or 4%, were found obscure even after autopsy (Southard[6]), although the problems in these 10 were later to some extent cleared up (Alford[7]). The causes in these obscure cases and in many cases in which the clinical diagnosis was proved erroneous were found to be infectious, toxic, somatic, non-nervous (*e.g.* streptococcus septicemia, streptococcus meningitis, cerebellar abscess). This work was of importance in prescribing work for the Psychopathic Hospital. The series showed that, where all diagnosticians came to agreement, the percentage of accuracy was about 9 in 10; that, where there was disagreement, somebody proved to have been correct in about 3 out of 4 cases; and that every diagnostician

was in the wrong in about 7% (17 cases), in the 250 cases.

5. The nature and causes of dementia precox. The organic nature of this disease was supported by the observation of gross or microscopic lesions in 86% of the unselected series investigated. The necessity of studying the anomalies and scleroses in these brains from a topographical point of view was shown. These results have prescribed much of the photographic and anatomical work since done under the appropriation (see below). The issue between the "mind twist" or psychogenic hypothesis and the "brain spot" or encephalogenic hypothesis came out clearly in the discussion of these findings at the Triennial Medical Congress, Washington, 1910.[8]

6. Geographical variations in the distribution of insanity. Two studies have been completed (a) as to towns,[9] (b) as to cities.[10] Surprising variability was found, more in the towns than in the cities. A rough correspondence was found to hold between the insanity rates (commitments) and the census rates (enumerations in 1905) of defectives, physical and social. The correspondence is closer between the rates for insanity and those for physical defectives.

SPECIAL INVESTIGATIONS UNDER THE APPROPRIATION.

7. The nature and causes of epilepsy and imbecility. The recent work on heredity, some of which had been done at Monson Hospital, working with the Eugenics Record Office, Cold Spring Harbor, Long Island, has tended to throw discredit on special causes such as infectious disease. This problem was attacked (Lu-

cas and Southard) from the other end: the after-history of children who had apparently recovered from poliomyelitis was followed. Proof was brought that cases of epilepsy could develop subsequently to such attacks of infectious disease.[11], [12] The heredity of these particular cases is now under investigation by a eugenics worker at the Psychopathic Hospital.

8. The nature of such mental disease as is consistent with normal or normal-looking brains. Statistical studies were made on Worcester Hospital material.[13] Previous results concerning the absence of evident brain damage in senile dementia (Danvers material, see paragraph 2 above) were confirmed with the Worcester material. The possibility was made out that there are two groups of dementia precox cases, a group subject to early death (often under two years), and a far more viable group dying as a rule at various ages eight or more years after onset. One brain in three was found to look normal in the Worcester series as against one in about four in the Danvers series. The problem of the normal looking brains in psychopathic subjects is of great importance, because the normal appearance of such a brain means either finer and largely non-destructive changes or else that the causes of the insanity in question reside outside the brain.[14]

9. The relation of mental diseases and defects to syphilis. Special work has been done with the Wassermann test to establish the percentage of syphilitics in various groups of patients (Worcester Asylum, 5 to 6%). The Essex County (Danvers) percentage of cases as received goes as high as 22% (study by H. L. Paine). The Psychopathic Hospital has occasionally received as high as 30% in a given

month. Three special pieces of work are in progress as to the relation of syphilis to mental disease: (*a*) Dr. A. Myerson of the Psychopathic Hospital staff is testing the merits of the Homer Swift treatment of general paresis by injections of salvarsanized serum into the cerebro spinal sheath. Progress in this work will be reported in the Notes on the Annual Conference for the Psychopathic Hospital.[15] (*b*) Dr. W. P. Lucas, formerly chief of the out-patient staff of the Psychopathic Hospital, is to report shortly on the general relations of the Wassermann reaction for syphilis to medicine, with special relation to mental disease. This paper will appear in the BOSTON MEDICAL AND SURGICAL JOURNAL as one of the State Board of Insanity Medical Contributions.[16] (*c*) It is contemplated, as material accumulates, to supplement the work mentioned under paragraph 3 above (errors in the diagnosis of general paresis) with statistical work on autopsied cases, showing the exact degree of improvement in diagnosis which has followed the introduction of the Wassermann method.

10. Nervous diseases of children and their bearing on mental defect. Lucas' work on congenital syphilis is of great importance here.[17] Boston City Hospital and Massachusetts General Hospital data, owing to the courtesy of the directors of their laboratories, have also been collected and given a preliminary analysis (N. K. Wood). This work will be published in due time, together with some studies of brain weight in children having a bearing on the effects of acute nervous disease.

11. Brain weights in normal and in insane subjects. To compare with insane hospital data, the data concerning brain and other visceral

weights from two large general hospitals (Boston City Hospital and Massachusetts General Hospital) have been collected and partially analyzed. Some data concerning spleen weights have been utilized by Dr. H. M. Adler, chief of staff of the Psychopathic Hospital, in his studies of the relation of the lymphoid apparatus, fat absorption, and insanity.[18] Data concerning a ratio termed the brain-trivisceral ratio (brain weight compared with combined weights of heart, liver, and kidneys) have been already published by Burns[19] (relation of brain weight to cancer) and have also been utilized in developing a conception of differential brain atrophy (atrophy of brain without similar atrophy of other organs, of paragraph 2, supra).

12. Anatomy of mental disease—statistical studies. Extensive tabulations of anatomical findings in mental disease, establishing tentative ratios of the normal to abnormal brains (appraised by available methods), have been made (see paragraph 8, supra). Use has been made of accumulated results in several publications (Southard[20]) and in directing research at the findings in the remainder of the body in normal-brain cases. It has been hoped thereby to clear the field for a study of mental disease, not attended by brain disease, if, as seems likely, there is such a group. Attention would thus be levelled upon the glands of internal secretion and other body organs.

13. Anatomy of mental disease—photographic studies. The most expensive and time-consuming investigation as yet undertaken under the State Board of Insanity fund has been the photographic and dissection work with brains. The brains studied now amount to about 500. The photographic work has been syste-

matic and uniform and permits a record of appearances, both before and after stripping the pia matter in the formalized brain, of the superior, inferior, left and right lateral, and left and right mesial surfaces. The work has been under the general supervision of the pathologist to the State Board of Insanity; the arduous dissection has been performed by Dr. Annie E. Taft, custodian of the Harvard Neuropathological Collection and appointed special investigator under the State Board of Insanity; and the photographic work has been done almost exclusively by Mr. Herbert W. Taylor. The work has been performed in the various laboratories from which the brains are derived and to which they are returned for safe keeping and in the neuropathological laboratory of the Harvard medical school. The brain photographs include, besides many from brains of the insane, photographs from fifty Monson State Hospital brains (epileptic) and a smaller number from the medical examiner of Suffolk County, Dr. George Burgess Magrath. A variety of studies, both qualitative and encephalometric, is being made from this collection (see next paragraph for example).

14. Anatomy in dementia precox. The photograph collection mentioned in the previous paragraph has been utilized most intensively so far in the study of dementia precox. In the prosecution of this study, made on Danvers State Hospital material (a continuation of work mentioned under paragraph 5, supra), frontal sections have been made and a photographic record taken of a sufficient number of the surfaces of section. From a combined study of the surface and section appearances, the sites of most extensive or markworthy lesions and

anomalies are mapped, and histological work is then carried out upon these areas and their fellows in the opposite hemisphere. In this way rapid entrance is effected into the problem of topical variations in the degree of destructive process going on. These topical variations will in future permit, or lay the basis for, an analysis of the correlation of structure and function in this most important group of mental diseases. The first results have been presented at the Triennial Congress of Physicians and Surgeons before the American Neurological Association at Washington, D. C., 1913, and at the International Medical Congress at London, Eng., 1913, and will be shortly published in this series of medical contributions.[21] An extension of the work to manic-depresive insanity, and other obvious extensions, will be carried out as time permits.

SUMMARY AND REMARKS.

A general picture is offered of the medical scientific activities of the State Board of Insanity of Massachusetts. The duty of investigation and publication as prescribed by law, and the special duties of the pathologist to the board are summarized.

A general summary of the various pieces of investigation before and after the special appropriation was made is given. It is estimated that over twenty-five workers have contributed to various aspects of the different investigations. The investigations are listed under fourteen heads, of which eight relate to work done subsequent to the special appropriation.

It is impossible that studies of this particular type and range shall be carried out without special funds, such as the New York Lunacy Commission and the Massachusetts Board of Insanity provide. It is hoped that other states will be prevailed on to establish a similar policy. The amount of money necessary for such investigations is negligible as compared with the money spent on maintenance; the results, however insignificant they may appear at a given moment, are bound to be some day of importance.

It is planned in future to publish various medical contributions from the State Board of Insanity in various appropriate journals with serial numbers such that readers may readily refer back to earlier contributions.

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XXX

A SERIES OF NORMAL LOOKING BRAINS IN PSYCHOPATHIC SUBJECTS.*

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(*From the Laboratory of the Worcester State Hospital, Worcester, Massachusetts.*)

CONTENTS.

I. Introductory Note.

II. Standards of Examination and the Problem of Normal-Looking Brains in Psychopathic Subjects.
  - Brain examinations never thorough enough to state that any brains are normal.
  - Brains should be considered normal until proved abnormal.
  - General pathologists have a blind spot for the nervous system.
  - Lesions, active and extinct.
  - Symptoms even of general paresis hardly explained by the lesions.
  - Importance of gliosis as indicating disease of some standing—the pre-indurative period.
  - Possible groups of normal-looking brains found in subjects of mental disease.

III. Forms of Mental Disease Associated with Normal-Looking Brains in the Worcester Series.
  - Worcester data show a higher percentage of senile psychoses in the normal-looking series than in the abnormal.
  - "Senile dementia," if associated with structural lesions, is in many cases attended by invisible and impalpable lesions.
  - "Normal-looking" brains and dementia præcox: contrast between the Worcester and the Danvers series.
  - Distribution of durations in the dementia præcox series—*dementia præcox brevis* and *dementia præcox longa.*

IV. Comparisons of the Worcester and Danvers Series of Autopsies.

V. Conclusions.

I. Introductory Note.

When it was deemed wise to mark the end of an era at the Worcester State Hospital by the collection of certain papers illustrating both work going on at Worcester and work by former

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* This paper forms contribution number eleven of the Worcester State Hospital (Mass.), Series of 1912, offered in compliment to Dr. Hosea Mason Quinby on the event of his retirement from the Superintendency after 20 years of service.

Worcester-trained men, I felt a desire to contribute something, not on the score of Worcester training to which I can lay no claim, but rather in the line of illustrating the value of careful scientific records and routine as carried on in a great state institution for the insane. Latterly, as pathologist to the Massachusetts Board of Insanity, I had enjoyed a certain supervision over the scientific side of the institution in the hands of my friend and colleague, Dr. S. T. Orton, pathologist to the Worcester State Hospital, and had become familiar with his and prior records, including those of Professor Adolf Meyer. I, therefore, conceived it to be of interest to study, in a large series of data from a fresh source, unbiased by any presuppositions of my own, *the problem of normal brains in subjects of mental disease.*

II. The Problem of Normal Brains in Mental Disease.

The practice of psychiatry outruns theory in one respect. For the practice of psychiatry recognizes that at least some victims of mental disease have normal brains. Psychiatric theory, on the other hand, is prone to say, *insanity is brain disease;* for, even if normal to all appearance, the brains of insane subjects must contain somewhere some theoretically demonstrable sign of disease.

I grant that it is desirable to investigate the brains of insane subjects *as if* their neurones were diseased. I should assert, without fear of contradiction, that no human brain has yet been examined, whether of insane or other subjects, with such thoroughness as to permit the statement, *this brain is quite normal.* I am even of opinion that, especially on the receptive side of the apparatus, few brains have been studied thoroughly enough with available technical methods.

But it can only be the rational part to *consider brains normal until proved not so.*

In my study, since 1906, of Danvers State Hospital brain material, I have focussed all attention on the problem of normal brains in mental disease. It is, strictly speaking, not easy to find a normal brain at autopsy, at all events in insane hospitals. It is also, despite the negativity of routine reports, not easy to find a normal brain in general hospital material, and it is especially difficult in medicolegal material.

There, however, enters the person of the examiner. Few general pathologists have had a thorough training in neuropathology, despite the fact that few other fields are so rich in recorded knowledge and in promise of knowledge. But a blind spot for the nervous system is cultivated by the pathologists, who proclaim their neurological ignorance with a pride almost fierce. Cornered they are prone to say that "so little definite is known," etc. All of which implies a complementary confidence in what *is* known concerning heart, liver, lung and kidney, which is astonishing. The result is that many brains dismissed as normal by the general pathologists prove abnormal on later review, anatomical or histological, and the impression has gained ground that *all* brains, at least of the insane, feeble-minded, or epileptic, will prove abnormal with the best technique.

In my personal series of autopsies, performed at the Danvers State Hospital, 1906-09, I was rarely able to find a normal brain according to my own standards of normality as demonstrable at the autopsy table. In a number of instances, however, extensive dissection proved requisite for the discovery of lesions, especially those affecting other regions than the cerebral cortex (*e. g.*, thalamus, dentate nucleus of cerebellum, etc.).

The abnormalities which I found, however, I could not feel were in all instances either causes or effects of mental disease. In several crucial examples I was able to prove microscopically a more extensive but milder lesion of perhaps a different locus than the naked-eye lesion. I, therefore, began to suspect that the gross lesions found were but promises of less severe (but perhaps more significant) lesions to be revealed by the microscope.

It is a fact that any severe cortical disease of fairly long standing is likely to be registered in the form of cortical induration or atrophy, diffuse or focal, of some degree. These scleroses, or the far more frequent atrophies, are perfectly possible of recognition by the interested pathologist and afford him significant guides in his microscopic research. It may conceivably happen that the focus of gross disease is no longer active and that the "symptom-producing" lesions are elsewhere and quite invisible to the naked eye. This latter state of affairs is perhaps not infrequent in dementia præcox (lower layer cortical gliosis) and in senile conditions (plaque-formation). In any event, however, the gross lesions which we find, whether active or extinct, are strong indicators of what may be found and usually is found upon microscopic research.

Brains with gross lesions of a sclerotic or atrophic nature are at least *suspect.* We cannot divorce ourselves from the conception that the brains are in some respect *significantly* abnormal.

But what are *significant abnormalities* of the brain in mental disease? No man can confidently say. General paresis is commonly regarded as the paradigm of mental disease attended with gross lesions. Are the gross or microscopic lesions of general paresis significant abnormalities? For the present these lesions are far from explaining, with any close correlation, the particular symptoms or even the general course of general paresis. Nevertheless we are likely to believe that the lesions found are theoretically capable of explaining the symptoms.

There is one obvious but neglected feature of brain tissue reactions which helps in correlation. Let the brain disease surpass a certain limit, and destruction of cells will follow. As a result of this cell destruction, the reparative reaction of the interstitial tissues known as gliosis is virtually, with certain peculiar exceptions, certain to occur. When it occurs it is likely, as above stated, to register itself in the form of palpable induration.

But this process of induration and eventual atrophy is by no means instantaneous and probably as a rule requires many weeks to reach a degree capable of being felt with the fingers at autopsy. Consequently a number of serious brain-cell disorders will fail to be recognized by the anatomist, if the subjects have died within the early or pre-indurative period. The anatomist would perforce term such brains normal when the microscopist would readily find changes of a serious nature.

With this hasty review of the problems of gross neuropathological anatomy we can arrange a tentative *à priori* classification of the

Possible Groups of Normal-Looking Brains Found in Insane Subjects.

1. Cases of mistaken anatomical diagnosis (small and central lesions or mild diffuse induration and atrophy are frequently overlooked).

2. Cases of mistaken clinical diagnosis ("not insane" cases dying of somatic disease in the insane hospital because it would have been hazardous to remove them therefrom).

3. Cases of mental disease of a type which usually shows structural brain disease, but which have not survived long enough to show either induration or atrophy (cases of early or very mild general paresis may show *no gross lesions but characteristic microscopic lesions,* and cases with marked fatty changes in the brain may exhibit no gross lesions in the pre-indurative period).

4. Cases of mental disease, of a type which may be conceived to exist, exhibiting neither observationally nor theoretically any brain lesion either gross or microscopic.

It is the establishment of the existence of this fourth group of *intrinsically normal brains* that psychiatric science needs for the purpose of directing research economically.

Are there mental diseases such that the brains on investigation prove in all respects structurally normal as only abnormal in that they permit or purvey the abnormal symptoms? *Can brain structures be intrinsically normal while extrinsically abnormal?*

If so, it would become curiously necessary for pathology to busy itself with *proofs of normality* rather than with proofs of abnormality in a series of structures.

III. Normal Brains at Worcester.

Of *249 cases autopsied* at Worcester State Hospital, Massachusetts, in the years 1895-1911, without the *observation* by the pathologist at the autopsy table of *gross visible or palpable lesions of the cerebral cortex,* there were (to judge by the assigned clinical diagnoses):

Senile dementia	67
Senile melancholia	7
Senile dementia with alcoholism	2
Senile paranoia	2
Senile dementia with epilepsy	1
Senile delirium	1
Total senile psychoses	80
Epileptic dementia	2
Organic dementia	1
Secondary dementia	1
Terminal dementia	1
General paresis	1
Total organic and other dementias, except dementia præcox and alcoholic psychoses	6

Manic depressive insanity	27
Melancholia	10
Involution-melancholia	8
Involution-psychoses	2
Circular insanity	2
Anxiety psychosis	1
Stuporous melancholia	1
Agitated melancholia	1
Hypochondriacal melancholia	1
Total manic-depressive group	53

Dementia præcox	42
Paranoic conditions	14
Essential dementia	1
Total dementia præcox group	57

Alcoholic insanity	5
Alcoholic delirium	4
Alcoholic deterioration	3
Alcoholic hallucinosis	2
Alcoholic mania	1
Delirium tremens	1
Total alcoholic psychoses	16

Epileptic insanity	5
Epilepsy	4
Imbecility	4
Idiocy	2
Imbecility and epilepsy	1
Total epileptics (non-senile) and imbeciles	16

Acute delirium	6
Toxic delirium	3
Delirium	2
Total non-alcoholic deliria	11

Constitutional inferiority	3
Hysteroid insanity	1
Huntington's chorea	3
Total	7

The separate larger groups might therefore be classified as follows, having in mind a general adherence to Kraepelinian lines:

Senile group	80
Manic-depressive group (melancholia included)	53
Dementia præcox group	57
Alcoholic group	16
Epileptic and imbecile group	16
Deliria, non-alcoholic	11
Miscellanea (hysterical insanity, Huntington's chorea, constitutional inferiority)	7
Organic dementia	6
Unrecorded	3
Total	249

GROUPS OF DEATHS IN QUARTER-CENTURIES.

	Cases
First quarter-century (actually 16-25)	18
Second	68
Third	120
Fourth (actually 76-91)	42

That there should be a group of 42 cases dying insane at ages between 76 and 91 and exhibiting intact brains on the autopsy table presents a significant problem. Many pathologists would wonder whether the brains of normal seniles should not exhibit some traces of atrophy, at all events in the higher eighties. And it would be only natural to suppose that the wear and tear of brains in the insane should lead to still greater atrophic changes.

Let us examine the assigned diagnoses in this *senile group* of subjects insane but intact of brain:

DEATHS OF INSANE WITH INTACT BRAINS, ÆT. 76-91		42
Senile dementia		32
Paranoic conditions	3	
Alcoholic conditions	2	
Imbecility	1	
Essential dementia	1	
Manic-depressive insanity	1	
Epileptic insanity	1	
Delirium	1	
Other diagnoses	—	10

Compare this with:

Deaths of insane with intact brains, *æt. 71-75*		22
Senile dementia	7	
Other diagnoses	15	

Either there is a crisis at which the psychosis senile dementia begins to be very frequent (consistently with intact brains), somewhere about the 75th year of life, or else the *diagnosis* senile dementia begins to be made with greater frequency about this crisis.

Comparing the incidence in the two hemidecades adjacent to this crisis, we find:

7 senile dements in 22 subjects æt. 71-75
19 senile dements in 27 subjects æt. 76-80

Before dismissing the problem of normal brains in senile psychoses, it is important to consider brain weights in the series, since the difficulties of naked-eye diagnosis do not always permit a ready evaluation of brain atrophy.

		Average.
Senile psychoses, *male*	49	1289
Brain weights above "average" (1357)[1]	12	1435
Brain weights below "average" (1357)	37	
Brain weights above 1265 ÷	28	
Brain weights below 1265	21	
Senile psychoses, *female*	25	1124
Brain weights above "average" (1235)	4	1318
Brain weights below "average" (1235)	21	
Brain weights above 1112 *	14	
Brain weights below 1112	11	

It is generally thought that the "averages," 1357 for male brain, 1265 for female brain, are too low, particularly in view of the fact that at least one of the component series of Vierordt's table, viz., Weisbach, 1866, includes brains with membranes removed. Accordingly it seems to be true that these cases exhibit weights too often below the "average," since almost any series of brains from general hospital material will show many cases with brains above Vierordt's "averages."

But there is stated to be a loss in brain weight varying with age. I have, therefore, tabulated these cases of senile psychoses, in accordance with the *probable* brain weights for their ages (Vierordt's combined tables), following a principle first adopted in some work done with Dr. Newell B. Burns at Danvers State Hospital.[2]

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* Lowest averages assigned to Europeans (pia mater removed), Weisbach, see above.

By this method, calculating all brains having below 98 per cent of the probable weight as of subnormal weight, I find that 40 out of 73 cases with brain weights available show brains with less than 98 per cent of their probable weights according to age.

Adopting another arbitrary standard, once in vogue, I found four cases having weights a sixth or more less than their probable weights.

7.2 , F., 62......... $\frac{995}{1210}=.82$ (percentage of prob. wt.)

9.54, F., 71......... $\frac{970}{1170}=.83$ “ “ “ “

9.83, M., 76......... $\frac{1010}{1290}=.78$ “ “ “ “

10.60, F., 68........ $\frac{890}{1210}=.74$ “ “ “ “

It may well be that these four cases should not belong in a group of "normal-looking" brains on the score of brain weight. Or we may possibly be dealing with a degree of microcephaly. In either case we should not be safe in considering these cases normal. If normal they must represent a deviation so extreme as to cause remark.

But six other cases show brain weights deviating more than 10 per cent from the average.

One of these,

7.53, M., 73.......... $\frac{1095}{1290}=.85,$

may belong with the extremely low weight series, but the others all belong within a range of 12 per cent of the average and are more likely to belong accordingly among the "normal," *i. e.*, not too extreme, deviates.

My general conclusion here is that four or five cases whose brains looked "normal" to the anatomist were with a certain probability abnormal (whether morbid or merely anomalous should not be risked). I remain with the impression that gross pathological anatomy has still to prove that *senile dementia*, as we use the term, is attended with any considerable loss of brain substance in a large group of instances.[3]

	Total.		Abnormal.		Normal-looking.	
Worcester series	741		492		249	
Senile psychoses	176	24 %	96	20%	80	32%
Manic-depressive insanity	36	4.3%	9		27	10%
Dementia præcox	42	5.6%			42	17%

These figures betray the curious fact that there is a higher percentage of senile psychoses in the normal-brain series (32 per cent) than in the abnormal-brain series (20 per cent). Another fact of interest (though here the figures are small) is that some of the manic-depressive brains seem to have been injured so as to show gross lesions but none of the dementia præcox brains.

Next to the problem of normal brains in the senile psychoses may be set the problem of normal brains in dementia præcox. The apparent normality of the brain in dementia præcox, or, to be more exact, the lack of startling gross alterations in dementia præcox brains, has led many persons to the conception that dementia præcox is a " functional " disease, either in the sense that no structural changes *have been* found in these brains or in the sense that none *will be* found therein.

We have seen that on this ground a huge proportion of senile dementias and other psychoses could be dubbed " functional " and in part perhaps properly so termed. We have also seen that the manic-depressive group is not at all free from a large proportion of cases with brain lesions (at least at time of autopsy), so that with equal propriety it might be argued that manic-depressive insanity is *not* a functional disease.

How then shall the apparent normality of 42 brains in dementia præcox be explained?

In one case (xv, 74) my colleague, Dr. Orton, was able to resolve the question satisfactorily by showing that the case was one of " brain death " (*Hirntod*) in Alzheimer's sense; in short, that the case, though possessed of an *anatomically normal* brain had a *histologically* quite *abnormal* brain. This case is to be published elsewhere.

The above case (xv, 74) had symptoms of but 15 days duration. Upon the general principle hinted at above (in the paragraph concerning the importance of gliosis), we should not expect *gross* anatomical evidence of disease in a case having such a brief total duration.

As a matter of fact 20 additional cases, *i. e.,* 21 cases or 50 per cent of the dementia præcox series, were cases having an assigned duration of less than two years.

The other 50 per cent of the dementia præcox group represent cases of, as a rule, much longer duration. In fact if we omit one case with assigned onset at 42 and death at 45 (xv, 50), very possibly a case of involutional character and another case, presumably of hebephrenic type with onset at 18 and death at 23, there are no cases with duration less than eight years. There appear, then, to be two groups of cases of dementia præcox, one group with durations of less than two years and another with durations as a rule eight or more years—a group of cases with small viability and a group having greater viability. Such a distribution may well indicate a somewhat critical character to dementia præcox, a tendency to a partition of cases into those in which the organism tends to go to pieces early and those of a more durable character. Incidentally it may be remarked that of 13 cases of katatonic type, but four belong in the "durable" group. Such a distribution, should it be confirmed by larger figures, might well emphasize that which perhaps goes without saying, viz., that katatonic cases are still more critical than others of the group.

When we compare this distribution in the dementia præcox group with that for the whole group of "normal-looking" brains, we find:

	Cases of less than 2 yrs. duration.	Cases of 2–8 yrs.	Cases of more than 8 yrs.
Dementia præcox	21	1(2?)	20(19?)
Whole group	85	81	82

It would be very desirable for all workers having access to extensive series of dementia præcox cases to study them from the point of view of *duration.*

Dismissing these incidental problems for the time being, it will be well to state what interpretation can be given to the "normality" of the brains in this series of dementia præcox brains.

In the first place half of them are cases of comparatively brief duration and may not have lasted long enough to change appreciably the size, shape, or consistency of the brain.

In the second place the analysis of these cases was not made with the knowledge of what was to be proclaimed so forcibly in later years, viz., that *dementia præcox is an organic disease.*

It will be remembered that some 86 per cent of the Danvers autopsy series of dementia præcox cases, viz., 24 out of 28 cases, were thought to possess structural lesions, either gross or microscopic.[4]

The disparity between the Worcester group and the Danvers group is at first sight striking; but it must also be remembered that, whereas 249/740 of the Worcester cases of mental disease (all types) showed normal-looking brains, only about 0.3 of the Danvers series could be safely put into that group. It is obvious, therefore, that different anatomical standards prevailed in the two laboratories. And it is especially valuable to have this statistical evidence of the degree of separation of these standards.

The question of duration is so important in the evaluation of the effect which a given disease may exert upon the brain that the whole distribution is presented, so far as it concerns 248 cases.

Duration.	Cases.		
3–12 months	26	36	85
3–12 months	10		
1– 2 years	49	49	
2– 3 years	26	47	127
3 years	21		
4 "	6	46	
5 "	9		
6 "	10		
7 "	5		
8 "	4		
9 "	8		
10 "	4		
11 "	2	34	
12 "	7		
13 "	4		
15 "	7		
16 "	6		
17 "	1		
18 "	3		
19 "	3		
20 "	1		
21 years	1	14	25
22 "	3		
23 "	1		
24 "	3		
25 "	1		
27 "	2		
28 "	2		
30 "	1		
31 "	2	11	
32 "	3		
33 "	1		
36 "	1		
37 "	2		
38 "	1		
40 "	1		
42 "	2	5	
43 "	2		
47 "	1		
50 "	2	6	
52 "	1		
53 "	1		
55 "	1		
78 "	1		

IV. COMPARISONS OF THE WORCESTER AND DANVERS SERIES OF AUTOPSIES.

The Worcester State Hospital series of autopsies in cases of mental disease, 1895-1911, numbered 740. The brains of 249 of these subjects, or about *one brain in three,* are recorded as of normal appearance on the autopsy table. A somewhat larger Danvers State Hospital series, similarly studied, had yielded something like *one brain in four* as of normal appearance in the gross.

As these *normal-looking brains* stand the best chance of corresponding with the so-called *functional* cases of *mental disease,* some effort has been spent on classifying the group from certain view-points, particularly those afforded by previous studies in the Danvers series.

Brains should perhaps be considered normal until proved abnormal, even if they belong to the subjects of mental disease. A review of the possible groups of normal-looking brains found in insane subjects leads to the supposition that there may be a certain group of such which will fail to show any lesion whatever: *there may theoretically, perhaps, exist brain-structures which, whereas* **intrinsically** *normal, are* **extrinsically** *abnormal.*

Before we arrive at a proof that such *intrinsically normal* brains can be found in psychopathic subjects, however, we must very carefully scrutinize our data.

It is well-nigh incredible that (as shown by the Worcester series) there is actually a higher percentage of senile psychoses in the normal-brain series, viz., 32 per cent, than in the abnormal-brain series, viz., 20 per cent. But a Danvers study had already shown the great variety of conditions covered even by the term senile dementia and had indicated that about one in every three so-called senile dements had a normal-looking brain. It would seem, then, that many of the senile psychoses, including a fraction of the dementias, are either functional diseases (in which the brain is intrinsically normal) or else based upon fine changes or limited changes not registered in the gross brain. The modern study of cortical "plaques" suggests a solution for at least part of this problem. In any case the facile pens which underwrite "arteriosclerosis" as a cause for everything must surely turn in some other direction.

Of course more finical search for lesions, such as diffuse or focal atrophies and indurations and various concealed lesions, might conceivably have altered these statistics by lowering the number of normal-looking brains. But the standard of normality also depends on the fear of attributing too great significance to minor anomalies or aplasias of the brain convolutions. To save the particular case from misinterpretation and overloading the slight apparent anomaly or lesion with too great functional consequence, the anatomist, however, is likely to throw into the normal-brain group various cases that look strange there. The general trend of psychiatry now demands proofs of normality in any brain of a psychopathic subject.

A less inevitable frailty of diagnosis is shown by these statistics in that patients over 75 years of age at onset are *far* more apt to receive the diagnosis senile dementia than those just under 75 years of age. After 75 the diagnosis senile dementia is surely too facile.

Another odd fact (at least in the writer's view, who had supposed manic-depressive insanity might prove exceedingly " functional " and to have brains only *extrinsically abnormal*) is the fact that one in four of the manic-depressive brains was in some respect grossly abnormal, whereas none of the 42 brains in dementia præcox exhibited gross abnormality. The latter finding is widely discrepant from Danvers findings in a similar series (where some 68 per cent of the series was thought to show gross cortex lesions and even 86 per cent to show gross *or microscopic* lesions).

The Worcester dementia præcox findings are perhaps in part explicable by the prevalent standard of anatomical diagnosis, anxious to avoid magnifying the importance of small atrophies or anomalies. It is also interesting to note that fully half the cases of dementia præcox autopsied at Worcester were of comparatively brief total duration (less and often far less than two years). Moreover nine out of the thirteen katatonic cases were in this brief-duration group: if the Danvers suspicion that the lesions of katatonia tend to be post-Rolandic is a well-founded suspicion, then another reason for missing the lesions can be adduced. In the writer's experience atrophic lesions of the posterior association area are most often missed, and similar lesions of the anterior association area most often neglected because so common.

The fact that these cases of dementia præcox are almost equally divided into a group with deaths two years or less from onset and a group with deaths eight or more years from onset suggests an inquiry to determine whether there may be two biological groups of these cases (the total series of all sorts of mental disease fails to show such a division).

Should this curious distribution of durations in the dementia præcox series be confirmed from other quarters it might prove possible to distinguish a *dementia præcox brevis* from a *dementia præcox longa* on grounds of differing natural history.

CONCLUSIONS.

1. The main object of this communication is to stimulate interest in normal or normal-looking brains in psychopathic subjects, so that the question whether insanity is, or is not, always a matter of structural brain-disease may approach settlement.

2. Normal-looking brains have now been found in a large fraction of senile dementia cases in two autopsy series, so that the "functionality" of these cases stands on as good a footing as that of various more generally recognized "diseases of mental function."

3. The issue in dementia præcox is now clearly defined, since one series (Worcester) might be interpreted to affirm the functionality, and the other (Danvers), to affirm the structurality ("organic nature") of the disease in question.

4. Incidentally the question has arisen whether dementia præcox may not on the ground of viability be divided into *dementia præcox brevis* (with early death, say under two years from onset; katatonic form often here found) and *dementia præcox longa* (in which the subject dies, as a rule more than eight years after onset, of a variety of causes; katatonic form less frequent).

5. Use has been made of a principle that apparent normality of brains may be consistent with fine microscopic changes, possibly of a reversible nature, and that we shall hardly from gross appearances be able to assert abnormality of brains unless at least three months (pre-indurative period) have elapsed from the onset of some cell-destructive process.

6. Use has been made of a principle to the effect that various nerve cells which are in all respects intrinsically normal may be essentially sharing in processes extrinsically abnormal.

7. The hypothesis is raised that the whole cortex, or even the whole nervous system, might be intrinsically normal but extrinsically abnormal in its reactions to a given chemical, physical or other condition.

8. It is possible that the solution of the problem of the functionality of various diseases might be to consider the structures involved as intrinsically normal whereas extrinsically abnormal—the normal operation of various cells leading to injurious effects in the organism as a whole.

9. It seems clear that the general statement *"insanity is brain-disease"* is well-nigh meaningless unless the particular structures thought to be involved are specified, since it is clear that science has not discovered even the right place to look in certain diseases (no more in mental disease than in certain forms of, say, diabetes).

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XXXI

CLINICAL AND ANATOMICAL ANALYSIS OF 25 CASES OF MENTAL DISEASE ARISING IN THE FIFTH DECADE, WITH REMARKS ON THE MELANCHOLIA QUESTION AND FURTHER OBSERVATIONS ON THE DISTRIBUTION OF CORTICAL PIGMENTS.*

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CONTENTS.

I. Introduction.
II. The General Distribution of Disease-Forms in the Fifth Decade Material (Danvers).
III Material and Methods.
IV. Case-Material (histories, post-mortem and microscopic findings).
  Female: Onset with depression.
    Onset with excitement.
    Onset with delusion.
    Other cases.
  Male: Onset with depression.
    Onset with excitement.
    Onset with delusions.
    Other cases.
V. Clinical Summary.
  Sex.
  Hereditary factors.
  Antecedent factors.
  General Clinical Features.
  Age at onset and at attacks. Duration. (Table.)
  Diagnosis.

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* Number 40, Danvers State Hospital Contributions.

VI. Anatomical Summary, with remarks on cortical pigment distribution.

VII. (a) The Relation of Arteriosclerosis to Fifth Decade Insanities.
  (b) The Relation of Senile Atrophic Processes thereto.
  (c) The Relation to Disorders of Internal Secretion.
  (d) The Relation of Fifth Decade Insanities to Manic-Depressive Insanity, to Dementia Præcox, and to Involution Melancholia.

VIII. Summary and Conclusions.

I. Introduction.

It is well to say at the outset of this communication that the facts presented—in either of the two main lines of consideration—cannot be fully understood until a similar analysis has been made of those insanities arising in previous decades. The two main lines of consideration are these: (1) an attempt to describe the chief clinical features of mental disease arising at different epochs in life and in some sense *genuinely* characteristic of said epochs, and (2) an attempt to secure a histological basis for metabolic changes and age-changes as shown in the distribution of certain special pigments in various types of cell (nerve-cells, neuroglia-cells, perivascular phagocytes) in subjects of different ages, as modified by the occurrence and duration of various mental diseases.

Both of these inquiries have been sketched in previous work from the Danvers laboratory. With H. W. Mitchell, one of the present writers (E. E. S.) read before this association in 1908 a paper entitled "Clinical and Anatomical Analysis of 23 Cases of Insanity Arising in the Sixth and Seventh Decades with Especial Relation to the Incidence of Arteriosclerosis and Senile Atrophy and to the Distribution of Cortical Pigments." Of course there is no reason to suppose that a division of human life into decades has any ultimate value as the basis of grouping morbid entities. But there is as yet lacking any other age-division superior to the decennial division, and it is clear that, if a complete analysis of a sufficiently large material from all the decades be made, no case-types will escape investigation and a picture of progressive disease-liabilities varying with age can be drawn. In point of fact, Southard and Mitchell had in a paper[1] preceding the one mentioned above (Melancholia with Delusions of Negation: three Cases with Autopsy) tried to investigate what has proved to be the main topic of the present paper, viz., involution-melancholia, by choosing cases on ordinary clinical grounds and endeavoring to decipher their cortex-histology. But the necessity of a broader field of view became at once apparent, particularly when we came to consider the distribution of pigments there studied.

But, although we had begun with clinical differentiæ (Cotard's syndrome) and desired to work especially on the cortex-metabolism (so far as histologically workable in the pigment field) in involutional insanities, we found that we had first to clear away the difficulties of the senile and subsenile period. In effect in their second paper,[2] dealing with insanity arising between 50 and 70, Southard and Mitchell felt that those senile and subsenile difficulties had been at least in part resolved. We stated categorically, on the basis of that study, that

> neither old-age changes nor arterial disease have any necessary connection with the development of insanity in the later years of life, at least in the sixth and seventh decades. It seems probable that *arteriosclerosis, senility,* and various forms of *insanity,* are entities which frequently interpenetrate, but are logically and genetically quite separate.

We were thus better prepared, as it were, to *climb down* from the senium and the subsenium to the still more obscure level of the pre- and post-climacteric in women and to the possibly allied difficulties in men as shown in the fifth decade (mental diseases arising from the 41st to the 50th year inclusive).

We need not rehearse in this introduction the tentative conclusions concerning pigment-distribution presented in either of the previous papers, but will speak further of them in our conclusions. They do not necessarily concern, either to strengthen or to invalidate, our clinical studies, but form a separate branch of biological inquiry taking their rise in the neglected field of Bevan Lewis (1890).[3] The work has been stimulated by the recent lipoid work of Alzheimer,[4] although his special methods have not been employed. We have dealt as before with certain pigments or pigment-like bodies brought out by the iron-hematoxylin method of Heidenhain.

We first present a condensed analysis of the total material from which our special material has been chosen, follow with casuistic analyses in the chosen series, and conclude with separate sections on the special and general problems touched.

II. The General Distribution of Disease Forms in the Fifth Decade Material.

From 871 consecutive autopsies (Danvers Series, No. 729 to 1600) we selected those in which the onset of the first mental trouble came in the fifth decade.

TABLE I.—MATERIAL.

No. 729 to 1600 of D. S. H. Autopsies.

Consecutive autopsies		871
Onset of insanity at 41 to 50		124
General paralysis	62	
Syphilis of brain	2	
Tumor	6	
Meningitis 1, septicemia 1, central neuritis 1	3	
Other coarse brain lesion; introductory shock	9	
Alcoholism	12	
No history	5	
Total ruled out		99
Leaving for consideration		25

A group distinguished by lack of all the above factors (the above factors are not peculiar to this decade).

We found that we had to deal with 124 cases arising between the ages of 41 and 50. Of these 62 were general paretics. There were two with cerebral syphilis, and six with cerebral tumor; one with central neuritis; one with meningitis; one with septicemia. These groups, 58 per cent, were laid to one side, with the feeling that not among them could the special characteristics of any decade be found. Five cases where no history could be found were added to these, leaving us with three groups, an alcoholic group, an arteriosclerotic group, and a remainder.

The alcoholic group of twelve cases we set aside because of the difficulty in locating the onset as well as on the supposition that here also little would be found of special interest for our chosen decade.

And lastly we separated out a group of nine cases where arterial disease was evident at the outset. Seven of these cases were post-apoplectic, one followed cerebral aneurism, and one began with hour-long periods of unconsciousness, convulsive attacks, death with gangrene and cerebral softening. With some reluctance we postponed the study of this group, but with the feeling that the cerebral insult masked the facts we were seeking.

Our remainder was found to consist of 25 cases which probably were associated neither with gross brain lesion nor with alcohol. Here, if anywhere, would lie the essential characteristics of psychoses of insanities arising in the forties. (See Table I.)

III. Material and Methods.

The special requirements of our investigation prescribed the material and methods used. We have, so far as possible in each case of the group chosen as above and described in brief in Section IV, considered carefully the following features:

(a) The *clinical history,* with especial reference to the age and character of onset (having practical prognosis particularly in mind), in women the relation of menopause to onset, and in all cases the duration of life and of mental symptoms.

(b) The *general autopsy findings,* as witness of general or special *metabolic disorder,* or *agonal* or *recent changes,* and of disorder of glands of *internal secretion.*

(c) The *condition of the gross brain,* as to the occurrence of softness, induration, atrophy (diffuse or focal), sclerosis, other focal lesions, and arteriosclerosis. With respect to the latter it will transpire that some few cases which gave no evidence whatever in the gross of arteriosclerotic disorder, exhibited extensive and important microscopic changes. These cases are duly noted below.

(d) The *condition of the brain cortex,* studied microscopically. The work here has no pretentions whatever to completeness and simply attempts to rule out or consider with particular care those cases where stains *for cell-topography* (*e. g.,* a monochromatic methylene blue stain) exhibit cell losses. Particular care was taken to consider the occurrence of changes reminding one of those in senile dementia and in dementia præcox. No special study of the occurrence and distribution of the Redlich-Fischer plaques has been undertaken for the present purposes. It is hoped to consider these lesions in a later communication in which the findings of the present paper can be correlated with those of Southard-Mitchell (1908).

(e) The *presence or absence and amount of* certain substances, here called *pigments,* demonstrable in the cortical cells by Heidenhain's iron-hematoxylin method after 95 per cent alcohol (or less advantageously) formaldehyde fixation. These have been studied in (1) *perivascular cells,* presumably i., as a rule about the larger vessels in cells of mesodermal origin (phagocytes), but ii., about some at least of the smaller vessels in cells of neuroglia type which resemble, if they are not identical with, satellite cells; (2) *neuroglia cells,* both in subpial layer and white matter and in the cortex-layers (satellite and other neuroglia cells); (3) *nerve-cells* of various types.

Remarks are offered in conclusion as to the possible significance of the quantitative and topographical variation of these iron-hematoxylin demonstrable lipoids. The study was conceived for the purpose of securing data concerning cortex-metabolism, using simple methods.

IV. Case-Material.

Case 1 is a married woman who had her first attack at 48 and died at 66 after four admissions to this hospital.

Her family history was negative.

At 48 she was apprehensive, suicidal, and had auditory hallucinations. Physical examination was negative. She was discharged as recovered.

On her return at 52, violent, agitated, depressed, it was noted that the menopause had been passed, but the exact time is left indefinite. After a period of sullenness, she became elated, then depressed again—always there was a trace of confusion. She showed exophthalmos and a very irregular and feeble heart. Again discharged as recovered.

At 56 she returned in an apparently manic confusion; she was cheerful and apprehensive by turns, and hallucinated. There was distinct exophthalmos, a pulse of 84, without enlargement of the thyroid; a tuberculin test was positive; albumen appeared in the urine. Discharged as much improved.

At 65 she appeared senile, dull, incoherent. She showed a great memory defect. Her heart skipped one beat in ten; there was much albumen in the urine. At 66, right sided shock with coma, death in two days (fever 102 at the time of shock).

Autopsy.—*The cause of death was cerebral hemorrhage.*

The brain weighed 1200 grams, and its substance was edematous. The basal vessels showed no sclerosis. The dura was everywhere adherent. The pia mater showed a slight general thickening, especially along upper border of cerebellum (spots of acute leptomeningitis). There was a hemorrhagic infiltration of the substance of the head of the left caudate nucleus and anterior third of the left internal capsule. (Staphylococcus pyogenes grown from area of hemorrhage.) Whether this was an area of encephalitis or a basal hemorrhage with invasion by staphylococci is doubtful.

Anatomical Diagnosis.

Hemorrhage in caudate nucleus and internal capsule (left).
Acute purulent pericarditis.
Acute purulent bronchitis.
Broncho-pneumonia.
Diploe densely congested.
Slight chronic leptomeningitis.
Marked external pachymeningitis.
Uterus much atrophied; many small fibromata.
Ovaries greatly atrophied.
Coronary and basal vessels smooth.
Aorta slightly thickened; a few small plaques.

Microscopic Examination.

Perivascular cell pigmentation slight or absent.

Neuroglia cell pigmentation moderate to marked universally in nerve cell layers, less in plexiform layer.

Nerve cell pigmentation variable within small areas, moderate to excessive in degree.

Nissl picture shows cellular gliosis of white matter and plexiform layer, moderate variable or absent satellitosis in nerve cell layers. Foci of cell destruction, apparently of a globular shape, without especial neuroglia reaction, characteristic though infrequent in layers of large external and medium-sized pyramids (frontal, occipital). Occasional large external pyramid caught in process of destruction with satellitosis. Edema changes in various layers, especially supragranular nerve cells in occipital sections.

Case 2 is a single woman whose mental illness began at 42, when she was brought to the hospital where she remained the rest of her life, dying at 50.

One of her sisters had fits. The patient had been a cheerful person of ordinary mental capacity.

During the menopause, at 42, she spent all night at the beach, "to hear the waves." The next morning she began to complain that an ointment had caused sickness everywhere, that bells and all street-cars had stopped because of it. Upon her entrance to this hospital a month later she still smelled the ointment "which had ruined the town"; "everybody in Lynn was afraid to go out"; she could hear the cries of her family who were being murdered. She was clear; her memory was good. The menses were irregular, she had hot flashes, the uterus was atrophied, there was a pustular eruption on back, chest, arms, fingers. After 3 months considerable albuminuria. In nine months a marked exophthalmos was noted, with a fine tremor, and pulse of 120, but no apparent thyroid alteration. In a year after admission she said that she was to be judge of the world. A little later a tuberculin test is reported as positive. Eighteen months from the time at which they were first noted, the exophthalmos and tremor had almost disappeared and her pulse was 90; her memory was good; "she did everything wrong." A general physical examination in the 7th year of her residence showed her condition as good.

Anatomical Diagnosis.

Disseminated tuberculosis of both lungs.
Chronic obliterative pleuritis.
Tubercular ulcers of ileum and caecum.
Chronic gastritis with healed ulcers.
Multiple thromboses of iliac and pelvic veins.
Atrophic liver (wt. 805 g.).
Chronic splenitis (wt. 35 g.).
Chronic diffuse nephritis.
Chronic myocarditis.
Slight mitral sclerosis.
Emaciation.
Ovaries atrophic.
Chronic external adhesive pachymeningitis.
Chronic leptomeningitis of vertex and cisterna.
Compensatory edema of pia.
Atrophy and sclerosis of frontal and central regions.
(Aorta, coronary and basal vessels smooth.)
Autopsy.—*The cause of death was pulmonary tuberculosis.*

The vessels of the base of the brain and elsewhere were of normal appearance. The dura was adherent to the calvarium at the vertex. The arachnoidal villi were moderately developed, particularly over the left central convolutions along the longitudinal fissure. The pia mater showed thickening over the veins in the neighborhood of the arachnoidal villi, and in the walls of the cerebellar cisterna, but nowhere else. The pia of the frontal poles and central regions of both sides contained considerable compensatory edema. The brain showed some variety in consistence, the frontal and central regions having most resilience, but was in general less firm than usual and suggested post mortem (30 hours) imbibition of water. The grey matter showed considerable pigmentation, especially of the vertex. The cerebellar laminae are slightly thinned out, most markedly in the clival and cacuminal regions.

Microscopic Examination.

Perivascular cell pigmentation moderate, more variation than usual in that the precentral tissue on both sides showed very little as compared with other areas examined. Some pigmentation of *endothelial* cells *in situ* in the left frontal region.

Neuroglia cell pigmentation moderate and universal in satellite cells of all layers (less in precentral gyri).

Nerve cell pigmentation not much in evidence except in the calcarine regions (more especially left) where there is considerable pigmentation, especially of the cells of the suprastellate layers.

Subpial fibrillar gliosis, especially calcarine. Nerve cells well preserved. Whether the development of arachnoidal villi on the left side can have anything to do with the greater pigmentation on the left side cannot be said. No special study of the convolutional pattern or of differential weights was made; it seems hardly possible to account for the differences on the two sides on a vascular basis. Perhaps we have caught a progressive unilateral atrophy in process. It must be remembered that certain dementia præcox studies indicate that the left cerebral hemisphere is somewhat more subject to anomaly than the right.

Case 3, a married woman, was admitted to this hospital at 50, recovered in eight months, was well at home for 24 years, and again came to this hospital at 73 to die in three weeks.

Her grandparents are reported normal, and her father. The mother, however, never recovered from an attack of melancholy which began at 48, and the only brother began to drink heavily when over 50. A maternal aunt was a senile dement. The patient herself was sensible, frank, cheerful, except for short spells of blues all her life. She had two children who are living and well, the youngest 35; menopause in late 40's with no mental symptoms. Development of right forearm arrested at three or ten years. At 49 received a burn which kept her in bed about a year.

At 50 she became depressed, hypochondriacal, suicidal, and was brought to this hospital. Soon recovering, the 24 following years found her "perfectly well both mentally and physically." In May, at 73, she was again restless and depressed, thought of suicide. In June, physical examination at this hospital showed a hardened radial, no tremor, a deformity of the right hand and arm (scar of burn), steadiness in Romberg's position, a right pupil slightly larger than the left. She was clear, apprehensive, self-accusatory, with flight: "I can't shed a tear," "my head feels as if it would burst," "are you going to cut my head, my arms and my legs off?" Symptoms of hemorrhagic cystitis appeared suddenly.

Anatomical Diagnosis.

Acute proctitis.
Acute metritis.
Hemothorax.
Chronic interstitial nephritis.

Arteriosclerosis of aorta, iliacs, coronaries, cerebral arteries.
Slight valvular endocarditis.
Hypertrophy of heart.
Much epicardial fat.
Chronic interstitial pancreatitis.
Chronic hepatitis.
Atrophy of spleen and stomach.
Lymphnoditis, retroperitoneal.
Cholecystitis, cholelithiasis.
Ulcer of colon.
Chronic interstitial fibrosis of lung.
Fibrous obliterative pleuritis.
Atrophy of mammary glands.
Central softening of adrenals.
Unequal pupils.
Frontal endostosis.
Subpial edema.
Clot in longitudinal sinus.
Chronic sulcal leptomeningitis.
Frontal gliosis and atrophy.
Temporal encephalomalacia (four hours post mortem).
Cyst of softening of left internal capsule.
Atrophy right lateral column.
Softening in sacral region of cord.
Dislocation of right wrist.
Arrested development of right hand.
Inequality in length of legs.
Anomalous ureter.
Anomalous blood supply of left kidney.

AUTOPSY.—*The cause of death was hemorrhagic cystitis.*

In connection with the brain findings, certain points need especial note; *endostosis of left frontal bone* near frontoparietal suture with erosion of corresponding dura mater and *maldevelopment of right forearm* (arrested probably at two to three years), with flaccid semiflexed hand and flexed fingers. The brain showed a small *white softening* (1 cm. in diameter) in the anterior portion of *left internal capsule* (no microscopic evidence of degeneration in the pyramidal tracts, examined in their passage through the bulb). *Bifrontal atrophy and sclerosis. Moderate internal hydrocephalus.* Brain weight 1195 grams. (Should weigh by Tigges' formula 1305 grams.) *Temporal* lobe tissues *soft.* (Microscopic examination showed marked edema changes, probably post mortem.) Unusually marked basal cerebral arteriosclerosis which microscopic examination indicates was part of a highly generalized process throughout the small vessels of the brain.

MICROSCOPIC EXAMINATION.

Nissl pictures show everywhere cellular gliosis of white matter and (marked) of plexiform layers. Generalized moderate perivascular cellular gliosis.

Considerable satellitosis, especially about large suprastellate layer cells on left side, highly marked on right side. Nerve cells much closer together on left side than on right in the superior frontal and precentral regions, not so in superior temporal gyri, conditions seem reversed in the calcarine sections. *Vessels* unusually *thickened* everywhere.

A special study with other methods would be necessary to determine whether the closely packed cells of the right pre-Rolandic sections mean aplasia or early loss (compare the maldevelopment of right arm and the endostosis of left side of cranial vault).

From the point of view of the present study, suffice it to say that there is little pigment of any kind in the Heidenhain sections except in the calcarine areas where especially the neuroglia cells are often somewhat heavily pigmented (more on left than right).

CASE 4 is a single woman who had her first mental illness at 47 and who died at 67, after 17 years hospital residence.

Her sister was insane. The patient from infancy had a paralysis of the left leg. She became a school teacher. The menopause was passed at 45 with insomnia, loss of appetite, pain in the head. She was subject to attacks of indigestion.

At 47 she came to an acute depression with recovery. At 50 she again was depressed, self-accusatory, suicidal, confused, dizzy, constipated, deaf. At times she claimed that "the dead were alive," "food was poisoned," "great estates were hers," "hands had grown to an immense size."

ANATOMICAL DIAGNOSIS.

Malformation of both legs.
Scoliosis.
Atrophy of interossei of both hands.
Contraction of palmar fascia.
Chronic fibrous pleuritis.
Pulmonary edema.
Atelectasis of left lower lobe.
Enlarged peribronchial glands.
Ascites.
Chronic adhesive peritonitis.
Acute fibrinous peritonitis.
Cholelithiasis.
Dilated common bile duct.
Hyperæmia of small intestine.
Thickened capsule of spleen.
Atrophy of uterus.

Tumor of uterus.
Cirrhosis of liver.
Slight atheroma of aortic intima.
Chronic nephritis.
Adherent dura mater.

AUTOPSY.—*The cause of death was peritonitis.*

The brain weighed 1040 grams and the thickened calvarium 365 grams. The dura is diffusely adherent to the skull but its inner surface is smooth. The vessels of the pia mater are engorged. No further description of the brain is available.

MICROSCOPIC EXAMINATION.

Little material is available in this case. *Frontal* sections show little or no *perivascular cell pigmentation,* a moderate amount in the *satellite cells* of the nerve cell layers, and proportionally rather more in the *nerve cells,* especially the larger pyramids. Moderate *subpial fibrillar gliosis.* The white matter shows little evidence of change. Considerable satellitosis, rather more marked in infrastellate layers (not fusiform) than in suprastellate, and some collections of satellites indicating total destruction of nerve cells, probably large pyramids. The second and third layers show a fairly even disappearance of nerve cells. The microscopic examination, taken in conjunction with the brain weight (1040 grams, should be 1185 grams by Tigges' formula), indicates a process akin to that of senile atrophic dementia.

CASE 5 is that of a married woman who first showed mental derangement at 42, who was brought to the hospital in three weeks and died after a month's residence.

Family history is vague and negative. At 30 her lover committed suicide; at 39 she was married. At 41 a uterine cancer was discovered; it was twice curetted; she lost 50 pounds.

Three weeks before entrance she became unusually silent and depressed, said that she did not want to be a burden, was discovered hunting for carbolic acid "which I might want to use." She was taken to a general hospital, where she was restless, out of bed, annoying other patients, immediately after a meal complaining that she had had nothing to eat. Here she showed no interest in her surroundings and was mute. Riggs' disease was found on the upper jaw; the thyroid seemed of usual size; there was no palpable sclerosis; the uterus was enlarged, fixed, its cervix rapidly breaking down.

ANATOMICAL DIAGNOSIS.

Chronic nephritis.
Sclerosis, moderate of aorta, slight of mammaries, aortic valve.
Fibrous myocarditis.
Chronic ventricular endocarditis.
Infarct of kidney.

Carcinoma of cervix uteri.
Metastatic growth in pelvis.
Slight acute proctitis.
Few enlarged inguinal glands.
Emaciation.
Scaphoid abdomen.
Atrophic breasts.
Left adrenal soft.
Bruises of scalp.
Calvarium thickened.
Chronic adhesive internal and external pachymeningitis.
Slight chronic leptomeningitis.
Patent foramen ovale.

AUTOPSY.—*Cause of death was chronic nephritis.*

Head.—Hair long, black, heavy. Scalp contains a large amount of fat. On inner surface of left temporal a bruise 3.5 x 4 cm.

Calvarium.—Frontal measures 4 cm., temporal 2 cm., occipital 7 cm. Scalp eburnated. No diploe.

Dura Mater.—Slightly adherent to the calvarium externally and internally along the longitudinal fissure. No marked development of the arachnoidal villi.

Pia Mater.—Thin and delicate except over the vessels and sulci. In superior portion shows slight milkiness. Slight cloudiness in fissure of Rolando and over the pons. Slight subpial edema.

Basal Vessels.—Show no sclerosis.

Pituitary.—Firm.

Sinuses.—Walled with cruor clot.

Brain.—Weight 1240 grams. Pons and cerebellum weight 140 grams. The brain is practically symmetrical. Convolutions for the most part well rounded. Slight flattening of the pre- and post-central gyri of right side; also in the left prefrontal a slight depression approximately 1 cm. in diameter. Brain everywhere firm: resilient. No ependymitis.

Cord.—Not unusual.

Middle Ears.—Left shows slight opacity.

MICROSCOPIC EXAMINATION.

No evidence of nerve cell losses, unless slight sulcal fibrillar gliosis of both superior frontal regions be taken to indicate damage to the plexiform layer. *Perivascular cell pigmentation* absent. *Neuroglia cell pigmentation* absent or slight except in both *calcarine regions,* where it is *marked. Nerve cell pigmentation* absent or slight (notably also, slight or absent in calcarine regions).

CASE 6 is a married woman whose first mental sickness showed at 44; came to the hospital at 45 and died at 46 after ten months residence.

Maternal cousin was insane and a patient here.

Patient was married at 26 to a quarrelsome man, who, for the last four years before her entrance, was sick. The only child of this marriage died at birth and since that time the patient has been hypochondriacal. For the last year the menses have been irregular, she has had hot and cold flashes.

At first she began to worry because she couldn't keep up the house and couldn't sleep; wished she was dead; everything seemed twisted; she suffered from headache. A month before admission she got the idea that the factory hands where she worked were going to carry her off and do something dreadful to her. Two days before admission she said that there was no God, and that she must go out in the streets naked. After a day of talkativeness she became mute for a few hours. She said to the examining physician, " Everything is wrong. There is nothing to cover me, so I have said there is no God. My head is going round."

Here the only thing remarkable physically was dorsal flexion on the right foot and no response on the left. She was restless, oriented, had difficulty in speaking, was depressed; at times confused and hypochondriacal. She became untidy and showed marked cloudings of consciousness. At times she was mute for a month; at times she repeated the same word over and over. Three months after admission there was marked tremor and she masturbated. She was given injections of goat lymph and ovarian extract without noticeable effect.

Anatomical Diagnosis.

Acute enterocolitis.
Lymphnoditis mesenteric and chronic.
Lymph nodes of groin enlarged.
Slight hydropericardium.
Acute nephritis.
Acute fibrinous pleuritis right.
Acute fibrinous parietal endocarditis left and (slight) right ventricle.
Fatty kidneys.
Spleen enlarged.
Cholelithiasis with obliteration of gall bladder.
Calcification of lower costal cartilages.
Arteriosclerosis, aortic, basal, arch.
Unequal pupils.
Atrophic ovaries.
Atrophic breasts.
Malformation of os uteri.
Malnutrition and anemia.
Slight chronic leptomeningitis, focal.
Atrophy of gyri, prefrontal, second and third frontal.

Autopsy.—*The cause of death was enterocolitis.*

The brain weighed 1105 grams. The vessels at the base were slightly sclerotic. The pia was slightly opaque over the posterior frontal and central regions and proximal halves of the Sylvian fossæ, clear elsewhere. The hemispheres were equal and roughly symmetrical. The gyri of both prefrontal and second and third left frontal regions were small: the collateral sulci and the openings of the Sylvian fissure were deep and flaring. The anterior halves of both hemispheres suggest pigmentation: on the left the first temporal gyrus is lighter in color than the neighboring Broca area, but there is no difference on the right.

MICROSCOPIC EXAMINATION.

Perivascular cell pigmentation everywhere even and very slight.

Neuroglia cell pigmentation moderate to slight everywhere. *Nerve cell pigmentation* little in evidence (Betz cells slightly pigmented).

No evidence of cell losses in areas studied, except that afforded by subpial gliosis (frontal, calcarine). The case deserves elaborate study from other points of view than those of this communication.

CASE 7, a married woman, who showed her first mental symptoms at about 46; came to the hospital at 59 and died about four months later.

Her mother was a senile dement. The patient was a normal child; hard working; honest. She was married at 33 and was always well until between 46 and 49, when the change of life came.

At this time she complained of being weak; thought there was something growing in her side; then grew physically weak for ten years. After this she made considerable mental and physical gains, and was able for three years to take charge of a small provision store. About a year before entrance she again became depressed and thought that she had a cancer; that her husband went with women; that people were stealing from her.

Here she showed edema under the eyes; regular weak pulse about 99; a heart not enlarged; arteries not thickened; a faint trace of albumen in the urine and many hyaline casts. She was tremulous and could not stand alone. Knee jerks and pupils were recorded as normal. She was disoriented, muttering, apprehensive, resistive, and expressed the idea that her food was poisoned. "O, I don't know much. They kept my brain and I didn't know they had changed the bed." Sometimes when touched she screamed as if in great pain; at other times pressure on the same spot brought no response. A month later irregular twitchings and muscular incoordination, sound associations, slight distractibility, memory defect for recent events, some tendency to fabricate. After a second month auditory hallucinations were evident; she was roughly oriented; feared that 72 pieces of skin would be cut from her back. At the end of a third month she was oriented and stated that her fears were imaginary, but that she could not help them. She complained of pain in her rectum and feared it might be a growth. "People think her wicked but she has never done any wrong." She was afraid of a dungeon and terrible fumes. During the last month she grew very weak, complained of pain in the left side and abdomen, and had constant hallucinations.

Anatomical Diagnosis.

Chronic mitral and aortic sclerosis.
Chronic perisplenitis.
Chronic appendicitis.
Chronic adhesive pleuritis, left side.
Chronic cystitis.
Renal lithiasis.
Slight arteriosclerosis.
Malnutrition.
Myomata of uterus.
Congestion of diploe.
Chronic pachymeningitis externa.
Slight subpial edema.

Autopsy.—*Cause of death was hypostatic pneumonia.*

The diploe was congested in patches in frontal and parietal bones. The pia over hemispheres and base was slightly edematous, clear and delicate. The basal vessels and their branches were free of gross changes, not conspicuous on section. The consistency of the brain substance was a little diminished; the convolutions rather plump.

Microscopic Examination.

Perivascular cell pigmentation in general heavy (in this case some comparisons were made with spinal cord pigmentation: little or no perivascular cell pigmentation was found in several levels examined), perhaps slightly less in some areas of the right side.

Neuroglia cell pigmentation heavy in most areas, perhaps more marked in left side sections.

Nerve cell pigmentation more variable in amount than what the other cell types show. Also in certain areas *some* of the *cells* are much more *heavily pigmented* than others. In general more on the left side.

Nissl pictures show many small *vessels thickened,* considerable *subpial gliosis,* and an increase of neuroglia cell nuclei within the cortical layers of the frontal sections (but these are apparently developed along capillaries rather than next to nerve cells). Little or no satellitosis about nerve cells. In the paracentral regions there are considerable stretches in which both suprastellate and infrastellate large pyramids are absent; but there is no evidence of satellitosis about the surviving cells. The precentral gyrus, left, shows numerous areas of focal atrophy, involving suprastellate layers, but leaving the first and second cortical layers. The remnant of nerve cells in these areas of devastation indicate that the process of destruction is a simple atrophy; there is never any evidence of satellitosis attending this atrophy.

Case 8 is a single woman whose first mental illness came on after the grippe and pneumonia, at about 49. She died after twelve years almshouse and hospital residence.

She had worked as cook; was cheerful; had good habits. Family history is unknown.

After her illness at 49, probably during the menopause, she became apprehensive, and soon developed auditory and visual hallucinations. Physical examination on her admission here showed a heart murmur and poor resonance over the right lung. She described her hallucinations quietly and intelligently. Later more emotional, she thought she was about to be killed. In three years she had gained much strength, and got into the habit of spending most of her time on a bench, scolding anyone who interfered with her. She was excitable, usually singing and noisy. After considerable improvement she was discharged to the almshouse at 54, and again returned to this hospital at 57, when she had a severe cystitis. At this time she was quiet when let alone, irritable when spoken to; disoriented, and said "I don't know" to everything. After several months in bed she developed erysipelas.

ANATOMICAL DIAGNOSIS.

Acute conjunctivitis.
Induration of skin of nose.
Acute hepatitis.
Acute parenchymatous nephritis.
Bronchopneumonia.
Epicarditis, acute.
Acute splenitis.
Myocarditis.
Chronic perisplenitis.
Chronic obliterative pleuritis,
Chronic interstitial nephritis.
Atheroma of aorta.
Valvular endocarditis, chronic.
Thrombosis of left ventricle.
Cavitation of apex of left lung.
Myoma uteri.
Unequal pupils.
Opacity of lens.
Chronic adhesive pachymeningitis.
Chronic leptomeningitis.
General cerebrospinal encephalomalacia.

AUTOPSY.—*Cause of death was erysipelas.*

Brain.—Hair, heavy grey. Scalp is unusually thick and contains much fat. Over the scalp about the roots of the hair are diffusely reddened areas, Temporal muscles are very small.

Calvarium.—Thin

Dura.—Fairly adherent to calvarium and the entire cranial wall. Is not adherent to pia. Pial vessels are deeply injected even to the finer branches.

Pia.—Is slightly milky along sulci. Pacchionian granulations along the longitudical fissure. Pia is not adherent to the brain substance. Basal vessels not remarkable. Brain weight 1085 grams. Brain is everywhere softened, especially at tips of frontal and the temporal lobes. There is a gaping of sulci in the parieto-occipital region of both hemispheres. Cerebellum and pons: weight 160 grams. The cerebellum appears softer than the cerebrum. No lesions noted. The pituitary body is softened and friable. Perforation of both ear drums.

Cord.—The pia is injected and cord unusually soft.

Microscopic Examination.

Perivascular cell pigmentation moderate everywhere.

Neuroglia cell pigmentation moderate to marked everywhere.

Nerve cell pigmentation moderate everywhere. The left side sections seem to show on the whole less pigment, especially the left calcarine.

Nissl pictures exhibit marked focal vascular lesions among which figure dilatations resembling those of *miliary aneurysms,* but there are no instances of hemorrhage and but few instances of focal glia reaction about the dilatations. There is, however, everywhere a heavy neuroglia reaction which is rather even in amount in the white matter but is on the contrary focally very variable in the plexiform layer. The *left precentral gyrus* shows good examples of focal destructive lesions of a suprastellate distribution, as if excavated under a comparatively well-preserved second cortex layer. Numerous other focal lesions and devastations. The veins of the cortex and the spinal cord are often packed with polynuclear leucocytes (erysipelas). Lime deposits in hippocampal gyri and in spinal cord (no sign of pyramidal tract sclerosis).

This case teaches how occasionally the gross appearances are surprisingly deceitful. The subject gave no coarse sign of arteriosclerosis or other vascular disease except plaques on the posterior aortic wall and aortic, mitral and pulmonic endocarditis. Yet hardly any cortex section is without evidence ofvascular disease.

Case 9 is a married woman, first insane at 46, who died six months later, after four months hospital residence.

Her father was insane. She had one child before her marriage at 34, four afterwards. She is now at the menopause.

Two months ago she became worried because she had married a divorced man and wanted to leave her husband. She became sleepless and apprehensive, depressed, self-accusatory. On admission here her knee-jerks were slightly exaggerated, the right more than the left; pulse 60, regular and weak. She complained of feeling weak and unable to eat; thought the doctor was going to shoot her, and that her children were to have their hearts cut out. After three weeks she failed rapidly; got so weak she could hardly talk; said that her stomach was full, she could hold nothing in it; was tube fed.

Anatomical Diagnosis.

Pneumothorax.
Hydropericardium.
Purulent otitis media right side (tuberculous).
Passive congestion of liver.
Mesenteric lymphnoditis.
Emaciation.
Atheroma of aorta, slight.
Granular ependymitis.
Brain weight 1260.
Constriction of stomach (6 cm. from pylorus, hour glass).

Autopsy.—*Cause of death was pulmonary tuberculosis.*

Brain weight 1260 grams. Calvarium shows a slight mottling of diploe. Dura and venous sinuses not notable. Pia clear and delicate over the hemispheres with delicate tracery of injected vessels. Basal vessels and cranial nerves not notable. Consistency of brain somewhat diminished. Convolutions full and with smooth surfaces. The ependyma covering the caudate nuclei and about the foramen of Munro is finely granular. Section of hemisphere shows rather conspicuous small vessels of cortex. Ependyma of fourth ventricle finely granular.

Microscopic Examination.

Perivascular cell pigmentation slight except moderate in frontal section.

Neuroglia cell pigmentation marked, except gyri recti.

Nerve cell pigmentation slight.

Nissl pictures show nerve cells fairly intact, with occasional moderate losses in suprastellate layers.

Case 10, a married woman, began to worry at 50 and died at 52, after residence in the hospital first for two months, and then for a year.

Of good family history, ambitious, a hard worker, she made an unfortunate marriage at 23. She had three children; she passed the menopause 49.

At 50, when her husband refused to work and planned to sell her home, she became sleepless, easily tired, unable to concentrate on her work, doubtful of her ability to do things. She took an overdose of laudanum. On entrance here the radial was sclerotic, the ankles edematous, while the urine showed albumen and casts. She had headache; was clear, oriented, inactive. After two months she made some improvement and was allowed to go home. Ten months later she was again admitted, inaccessible, irritable, with nothing suggesting hallucinations, and a frequent complaint of a queer feeling in her abdomen. At this time physically she showed an enlarged heart, a soft radial, blood pressure 105, a negative urine. During the last month of her life she was very weak and at times delirious.

Anatomical Diagnosis.

Very slight arteriosclerosis of internal mammaries, coronaries.
Thickening of aortic and mitral valves.
Chronic endocarditis.
Fibrous myocarditis.
Chronic parenchymatous nephritis.
Chronic passive congestion of liver.
Caseous nodule of right lung.
Apical scars of both lungs.
Chronic bronchitis.
Chronic obliterative bronchitis.
Lymphnoditis, superficial, mesenteric, retroperitoneal.
Injection of ileum.
Omental adhesions.
Fibroid of uterus and endometritis.
Sclerotic ovaries.
Slight chronic lepto- and pachymeningitis.
Slight asymmetry of brain.
Unequal pupils; cataract of right eye.
Poorly nourished.
Decubitus elbows; sacrum; acromion, right and left.
Muscles pale.
Bone marrow pale.
Scar of right thigh.

Autopsy.—*Cause of death doubtful.*

The brain weighed 1155 grams. Generally of about normal consistency, the right angular gyrus was the softest portion. The convolutions were well rounded. The right hemisphere was 1 cm. shorter than the left.

Microscopic Examination.

Little or no pigment except in the neuroglia cells of the calcarine cortex. No evidence of cell losses.

Case 11 is a single woman whose first mental trouble came on at 44. She died at 48 after three years' residence in this hospital.

A second cousin is insane. The patient has been a cheerful woman of ordinary mental capacity and able to support herself. In the late thirties her menses became irregular, and in June of her 44th year they ceased altogether.

At the latter date came insomnia, self-accusation, hallucinations, visual and auditory; after ten months without improvement she was brought to this hospital. Physical examination on admission showed impaired resonance of lungs, an increase in knee-jerks and a slight ankle clonus of left foot, and tremor of hands and face. She was oriented, restless, apprehensive. She said, "I have abused myself," "I am paralyzed," "The clock is fixed to take care of my brains and that means I am not to get well," "Everything seems queer and far off and dull," "I know these things are not so but I can't help thinking of them." One instance is recorded of opisthotonus following a "pain in the head." In about three months came a change to a silly, violent mood, compulsive ideas. "I am not able to make people understand how good I have been." "Keeping in trouble all the time is the only way to make things straight." This mood continued, with good orientation and memory, to her death at 48, from swallowing a cloth.

Anatomical Diagnosis.

Hemorrhage, congestion and edema of lungs.
Acute congestion of spleen and kidney.
Chronic perisplenitis.
Cyst of left parovarium.
(Vascular system apparently normal.)

Autopsy.—*Cause of death was asphyxia.*

The brain weighed 1310 grams and beyond a general edema was not noticeable in the gross. The pia was clear. The basal arteries were free from gross changes.

Microscopic Examination.

Perivascular cell pigmentation somewhat more variable than usual (much in right frontal region).

Neuroglia cell pigmentation variable (more in right frontal, left precentral, about the same amount in both calcarines).

Nerve cell pigmentation marked in frontals and calcarines, little in precentrals (but marked variation from cell to cell).

Nissl pictures suggest, but do not clearly show, moderate cell losses in suprastellate region (layers of medium-sized and larger external pyramids).

Case 12, a widow, came to this hospital at 47 for two attacks of mental trouble, and then returned at 65 to remain for ten years.

Her mother died of asthma; an aunt was insane. The patient was a cheerful woman.

At 47, in the menopause, she complained of pain in the top of her head, was depressed and self-accusatory, improved; six months later grew worse, thought the family were going to be burnt, had auditory and visual hallucinations. She was very feeble. Improving again she was allowed to go home, where for eighteen years she "had spells of thinking herself on fire and wanting to jump out of the window." On returning to this hospital at 65 she was well nourished; her knee-jerks slightly increased. For the first few weeks oriented, quiet, silly, rambling in her talk, she became confused, noisy, hallucinated, doing things on impulse. A three months' period of complaints about having heart disease followed; then three months when she was quiet, well behaved, industrious. In the three following summers she had mild manic attacks, with intervals of clearness and quiet. Six years after entrance she failed rapidly after much digestive disturbance. Memory defect for recent events appeared. In the seventh year came a manic attack; in the ninth she withstood an attack of lobar pneumonia, but two months after complained of dizziness. In the tenth year her pupils were small and did not react to light or accommodation; she showed good insight, memory, judgment to the time of her death from a sudden attack of edema.

ANATOMICAL DIAGNOSIS.

Edema ankles, eyelids, ascites.
Abscess of kidney.
Chronic nephritis.
Milk patch.
Vegetative endocarditis.
Basal sclerosis.
Chronic sclerosis.
Chronic peritonitis.
Chronic perisplenitis and perihepatitis.
Mesenteric lymphnoditis.
Sago spleen.
Apical scar.
Bronchial lymphnoditis.
Chronic fibrous pleuritis.
Chronic pachymeningitis.
Chronic leptomeningitis.
Dural tumor (small).
Bone marrow pale.

AUTOPSY.—*Cause of death was acute nephritis.*

The brain weighed 1310 grams. The dura was generally thickened and over the occipital region in the medium line presented a tumor 1 cm. in diameter. The pia was injected and slightly cloudy. The basal vessels showed areas of sclerosis. Convolutions, well rounded, showed shallow depressions in the supraparietal regions.

MICROSCOPIC EXAMINATION.

Perivascular cell pigmentation moderate and even throughout.

Neuroglia cell pigmentation marked, and especially marked in precentrals.

Nerve cell pigmentation moderate, but perhaps somewhat more in left precentral than elsewhere. No certain evidence of cell losses in areas so far examined.

CASE 13 is that of a married woman who first became insane at 43 and who died at 68 after a hospital residence (very much interrupted) of about ten years.

Her uncle was insane; her sister and a son died of tuberculosis. She is described as cheerful.

At 43, after a long siege of nursing, she began to complain of headache, said she was Jupiter, under the control of her son's spirit, possessed of unbounded wealth. Noisy, incoherent, elated, fantastic, when she came to the hospital, she recovered in twenty-four days. Six months later she came to the hospital in another attack—this was like the first except that hallucinations of sight and hearing were noticed. She came in for six more attacks before she was 50; in the intervals she was progressively more demented and indecent. At 63 she was admitted for the last time, with a temperature of 101, an enlarged heart, a systolic murmur; her knee-jerks lively. She was clear and dressed in bright colors. "I am not a common insane patient." She stuttered and slurred in her loose, stereotyped talk. Six months before her death the urine showed red cells and albumen; at this time she began to vomit and from then on symptoms of gastro-intestinal origin were prominent. She was well oriented to within a few days of her death.

Anatomical Diagnosis.

Edema of left ankle.
Jaundiced skin.
Purulent bronchitis.
Acute cystitis.
Chronic periappendicitis.
Chronic peri-oophoritis.
Splanchnoptosis.
Chronic fibrous pleuritis.
Chronic fibrous epicarditis.
Sclerosis of coronaries, basal, aorta.
Chronic interstitial nephritis.
Atrophy of spleen.
Infarction of lung.
Purulent otitis media.
Purulent mastoiditis.
Unequal pupils.
Pigmentation of trunk.
Emaciation.
Calvarium dense.
Chronic fibrous pachymeningitis.
Chronic fibrous leptomeningitis.
Injection of pia mater.
Subpial edema.
General cerebral atrophy.

Autopsy.—*Cause of death was carcinoma of stomach and pancreas.*

Calvarium.—Frontal measures 0.6 cm., temporal 0.4 cm., occipital 0.9 cm. Is smooth, eburnated externally, internally wrought with deep grooves for the meningeal vessels. Orbital surfaces rough and prominent. The markings in the middle cranial fossa are prominent, amounting almost to exostoses. Diploœ present.

Dura Mater.—Slightly thickened everywhere. Adherent in the post cranial fossa. Sinuses negative. Pacchionian bodies medium sized.

Pia Mater.—Bound to dura by a few adhesions at the frontal and temporal poles, is slightly thickened in the Sylvian region and over the inferior surface of the cerebellum and post cisterna. Pial vessels injected over the whole convexity. There is a marked subpial edema in all parts of the convexity (hydrops ex vacuo).

Brain.—Weight 1105 grams. The convolutions are atrophied in the frontal, central, parietal and occipital regions. The consistency in all parts is decreased, with more marked decrease in the parietal region than elsewhere. No granules in the ependyma of fourth ventricle or lateral ventricles.

Basal Vessels.—Show scattered areas of thickening in the different branches, but nowhere marked except in the carotids, which are diffusely thickened, but not calcified. The smaller cortical vessels are not thickened. Artery to the right corpus striatum shows a small atheromatous patch.

Pons and Cerebellum.—Weight 140 grams. Cerebellum everywhere softened. Pons decreased in consistency. Medulla normal.

Microscopic Examination.

The *pigmentation* of all cell types in the chosen regions is everywhere remarkably slight.

Case 14 is that of a single woman whose insanity began at 45, who was brought to this hospital at 56 and died in ten days.

Always peculiar and seclusive, after the menopause at 45 came recurring episodes of delusions of persecution, followed by nearly normal intervals. In the attack for which she was brought here she claimed that everything had a bad odor, at one time fell to the floor, trembled, frothed at the mouth. Here exophthalmos, pulse 124; allowed needle to be stuck into eye and tongue without affect. She was mute, resistive, tube-fed.

Anatomical Diagnosis.

Edema and congestion of lungs.
Chronic diffuse nephritis.
Fatty myocarditis.
Valvular sclerosis.
Edema of lower legs.
Chronic localized peritonitis.
Chronic caseous lesions of spleen.
Pigmentation and fatty change of liver.
Scars of right apex.
Basal, coronary, valvular, sclerosis.
Encephalomalacia sixteen hours.
Chronic fibrous leptomeningitis, Rolandic.

AUTOPSY.—*Cause of death was bronchopneumonia.*

The brain weighed 1245 grams. The occipital poles and temporal regions were slightly softer than the remainder of the brain. The pia was moderately injected and was opaque over both Rolandic regions. The vessels at the base showed a few patches of sclerosis which were not present in the primary or distal branches.

Nissl pictures show the left superior frontal gyrus poorer than right in nerve cells, and the left precentral poorer than the right, with foci of subpial gliosis. In the superior temporal gyri the stellate cell layer of the left side is not so rich in cells as that of the right side. Hippocampal gyri: The left side section shows a focus of nerve cell poverty in the giant cell layer of the fascia dentata; the ependyma shows a general thickening without small breaks and in places is normal for long distances; there is a suggestion of focal cellular gliosis in the polymorphous cell layer. In general many axonal reactions are demonstrable in the frontal (large external pyramids) and precentral (Betz cells) regions. There is, however, some evidence of a greater long standing atrophy and gliosis of the anterior regions.

MICROSCOPIC EXAMINATION.

Perivascular cell pigmentation everywhere moderate to marked.

Neuroglia cell pigmentation marked as a rule.

Nerve cell pigmentation chiefly in layers of medium size and large external pyramids. The precentral areas show occasional Betz cells highly pigmented, others not at all.

CASE 15 is that of a single woman of 48, whose mental trouble apparently began a few years before admission. She died after twenty-five days' residence.

At 44 she began to have fits, she slept in the day and was awake most of the night; her weight was 250. A dementing process followed. On admission here she was weak, drowsy, stupid, deaf, partly oriented, her memory poor for recent but fair for past events. In two weeks she showed more interest, complained of being lonesome. At any time a rational answer to a simple question could be obtained if the questioner could break through her drowsiness. She had considerable insight. Her voice was rough and expressionless. Physically the picture was that of myxedema: wide nose, thick, everted lips, large tongue, stubby extremities, edematous appearing skin with no pitting, loss of hair. There was a systolic murmur, weak thready pulse, many syncopal attacks. A few days before her death appeared symptoms of an acute infection of the urinary tract.

ANATOMICAL DIAGNOSIS.

Pulmonary edema.
Internal hemorrhagic pachymeningitis, right convexity.
Recent hemorrhages, subdural space.
Atheroma of aorta.

Fatty infiltration of heart muscle.
Chronic fibrous endocarditis.
Chronic fibrous pleuritis.
Hyperemia of spleen.
Fatty degeneration of liver.
Hyperplasia of thyroid.
Myxedematous hypertrophy of skin.
Panniculus dry, pale.
Hypertrophy of calvarium.
Cerebral atrophy, chiefly frontal.

AUTOPSY.—*The cause of death was kidney abscess.*

The calvarium weighed 450 grams. Between dura and pia was a thickened hemorrhagic membrane extending over the right hemisphere and depressing the cortex anterior to the Rolandic fissure. The cortex here had a necrotic appearance. At the base of the middle fossa was a small area of hemorrhage. The pia was notably thickened along the cranial nerves and vessels, very slightly thickened over the convexity; it was quite generally adherent to the cortex and could only be removed in small pieces; it was not especially cloudy; over the left hemisphere it was edematous. The basal blood vessels showed no notable changes. The convolutions in frontal and parietal regions were slightly atrophied; the surfaces of many of the frontal ones showed fine depressions and lines of contraction.

MICROSCOPIC EXAMINATION.

Perivascular cell pigmentation slight to considerable.

Neuroglia cell pigmentation slight, except fusiform layer of left calcarine and lower layers of right calcarine areas.

Nerve cell pigmentation slight except precentrals, which vary, some cells negative, others supplied with an excess.

Nissl pictures.—Progressive changes in glia cells of all regions; increase of glia in superficial layer and in white substance; nerve cells in parietal region shrunken and in pyknomorphous condition; no active degenerative processes; leucocyte accumulation in many of the smaller arteries; hyaline degeneration of cerebral capillaries in all regions.

CASE 16 is that of a man whose first mental symptoms appeared at 47, who came to this hospital three years later and died after one month's residence.

His father was probably a suicide. He himself had been a steady worker, a moderate drinker; he had had inflammatory rheumatism, probably gonorrheal, at 24 and 27. From 35 to 47 he had many morning headaches; at the latter age he gave up drinking.

At 47 he became restless, sleepless, refused to see anyone, refused to eat, complained of a pressure in his head and a shaking in his bowels; later he developed hallucinations of sight. He thought that he was dead and the cause of all people's deaths. At 50 he improved considerably and went to work for three months; then became over-talkative, claimed to have found a new tinning process, was boastful and elated. On entrance there was albuminuria. He showed flight of ideas, elation, hallucinations of hearing, perfect orientation. Three weeks after admission he was taken sick with dysentery and died five days later.

ANATOMICAL DIAGNOSIS.

Acute ulcerative colitis.
Lymphnoditis mesenteric, retroperitoneal, bronchial.
Thickened mesentery.
Fatty liver.
Chronic interstitial nephritis.
Bronchopneumonia.
Ventricular endocarditis.
Coronary and slight basal sclerosis.
Chronic fatty myocarditis.
Slight hypertrophy of heart.
Chronic perisplenitis.
Hypertrophy of prostate.
Emaciation.
Slight internal hemorrhagic pachymeningitis.
Slight leptomeningitis.
Encephalomalacia of temporal lobes (7.5 hours post mortem).
Perforation of left ear drum.

AUTOPSY.—*The cause of death was dysentery.*

The brain weight was 1450 grams. The dura was not adherent to the calvarium but to the pia over the vertex and along the longitudinal fissure. The pia, over the central and superior parietal gyri, was reddened; it was thickened over the sulcal vessels; it stripped readily from the cortex. The convolutions were well rounded except for the superior parietal gyri, which were small and depressed below the surface level. Brain substance firm, the temporal lobes a trifle softer than the rest. Ventricles are smooth; the choroid plexus slightly cystic. The frontal region on section retracts from the knife and the gray matter over the crowns of the gyri is china-white. The white matter shows many small bleeding spots.

MICROSCOPIC EXAMINATION.

Satellitosis is a fairly marked feature in a few areas of cell losses. *The perivascular cell pigmentation* is almost wanting. *Neuroglia and nerve cells* show it in slight degree.

CASE 17 is that of a man whose insanity came on at 45 and who died in this hospital after seven months residence.

His father died of apoplexy at 58, and father's brother had epilepsy. Otherwise family history is negative. Patient himself was a good worker, earning $1200.00 a year; of a nervous, conscientious sort. He admitted having clap, but denied syphilis.

A year before entrance he became tired and unable to sleep; gave up his work; said that he was sick and not good for anything. For a month before entrance ideas of self-reproach occupied his mind. "Am not even good enough to kill myself." On admission here his arteries were fairly palpable; heart seemed normal in size; soft systolic murmur; pulse of high tension; visible radial pulsation; urine showed a slight amount of albumin; epithelial and hyaline casts. His hands showed a slight tremor; his knee-jerks were very much exaggerated. He was clear, agitated, sleepless, despairing. A week after admission his temperature was 101. He said, "I am unable to talk. Everything is blank to me. I have no memory; no friends; my bowels do not act." In a few weeks he manifested delusions of somatic character. A month before his death he said, "I haven't a home or a wife; how could I support a wife?" After falling to the floor he remained in a dazed, apathetic, stuporous condition for a few days; developed paralysis on the left; died.

Anatomical Diagnosis.

Cerebral hæmorrhage—right lateral ventricle.

Hæmorrhage beneath scalp.

Arteriosclerosis of internal mammary, iliac, basal, coronary arteries and aorta.

Chronic epicarditis.

Thickened aortic valve.

Endocarditis.

Hypertrophy of heart.

Acute pleuritis.

Bronchopneumonia.

Acute bronchitis.

Ulcer of neck.

Emaciation.

Calvarium eburnated.

Slight chronic pachymeningitis.

Cyst of pituitary.

Slight subpial edema.

Autopsy.—*The cause of death was cerebral hemorrhage.*

The brain weighed 1395 grams. There was a marked flattening of the convolutions over the parietal portion of the right hemisphere, and this area showed a lessened consistency.

Microscopic Examination.

Perivascular cell pigmentation in general slight, except precentrals, where it is marked.

Neuroglia cell pigmentation everywhere considerable, but very well marked in precentrals and calcarines.

Nerve cell pigmentation in general slight, except precentrals.

Case 18, a married man, had a first attack at 43 and died at 46, after a three years' interrupted residence at this hospital.

A sister of the patient had chorea when young; another sister is very nervous.

The patient himself was a very steady worker; at 42 he was working night and day. He complained of several attacks of blindness of short duration, of nausea, of sciatic rheumatism. At one time he left the house and said that he was going to cut his throat; he would grasp violently at his throat; he tried to strangle his wife and then asked forgiveness. A local physician found something wrong with the kidneys after the patient had complained about them. He tried to work, but couldn't He saw knives and razors lying about the bed and had an uncontrollable desire to handle them. On entrance he showed a large heart, albumen in the urine, a fine tremor; he complained of a gagging sensation in his stomach immediately after eating, insomnia, weakness, buzzing in the head. He asked to be restrained so that he could not hurt anyone. After two months he felt better and went home. After three months he returned, fearing that he might harm someone, complaining of peculiar dull aches in his head with intervals of feelings of "head emptiness," giving a history of dizziness and (doubtful) auditory hallucinations. Here he showed ataxia, exaggerated knee-jerks, pupils reacting rather sluggishly to light and well to accommodation. Within a month he developed slurring articulation and auditory hallucinations; he misplaced words in test phrases, grimaced before the mirror; wanted "remedies for his brain." In September he made a good recovery from dysentery. In October, with many symptoms of tuberculosis of the lungs, he became more cheerful. In December after a bad attack of psoriasis he was still better mentally; his urine contained, as always, a few hyaline casts. In February came pains in his left leg, which became swollen to the thigh. At this time the notes say, "Patient constantly has hypochondriacal attacks, demanding medicine." On March 1 his temperature was 102, on March 4, 104. Throat culture for the K-L bacillus was positive. He was confused; had ataxia and tremor; died.

Anatomical Diagnosis.

Cerebral hæmorrhage.
Bloody discharge from nose.
Acute tracheitis and bronchitis.
Acute nephritis.
Acute splenitis.
Puriform thrombus of right transverse sinus.
Hæmorrhagic ganglionitis.
Softening of pituitary.
Cyst of the cerebellum.
Cortical destruction, occipital and temporal left.
Acute leptomeningitis.
Hæmorrhagic ileitis.

Tuberculosis right lung.
Scar at apex left lung.
Thrombus left popliteal vein.
Edema left foot.
Exudative pharyngitis and tonsillitis.
Hydropericardium.
Tricuspid and ventricular endocarditis.
Chronic fibrous myocarditis.
Hypertrophy of heart.
Hematoma of eighth rib.
Constriction of œsophagus.
Eversion of tip of ensiform.
Moderate splanchnoptosis.
Chronic perisplenitis and perihepatitis.
Chronic fibrous pleuritis.
Mesenteric lymphnoditis, pancreatic group.
Unequal pupils.
Hypertrophy of prostate.
Calvarium thin.
Chronic adhesive external pachymeningitis.
General cerebral gliosis.
Sclerosis of occipital veins, left.
Arteriosclerosis of posterior basal vessels; and left superior cerebellar arteries.

AUTOPSY.—*The cause of death was cerebral hemorrhage.*

The brain weighed 1475 grams. The dura was slightly thickened and very adherent to the skull. The meningeal branches of the occipital veins are visibly hyperdistended and on the left side notably thickened. The basal vessels are thin and delicate. The hemispheres are equal and the consistency increased. Over the inferior surface of the left occipital and posterior temporal lobes occurs a diffuse hemorrhage which destroys the cortex and extends into the gray matter for 2 or 3 cm. On the right side in the same area injection surrounds the distribution of the porterior cerebral artery. There is a cerebellar area of softening 2 cm. in diameter. The left superior cerebellar artery is thickened and of unusual size. The Gasserian ganglions are hemorrhagic. The pituitary was soft with a minute area of softening in the center.

Microscopic examination of the small amount of material available shows *nerve cell pigmentation* exceeding that of *neuroglia cells,* while the *perivascular cell pigmentation* is negligible.

CASE 19 is a man whose insanity began at 49 and whose death occurred five months later after less than three months' hospital residence.

The father was eccentric, and there were instances of insanity on the paternal side.

After considerable loss of money mental symptoms appeared in the following order: Worry, insomnia, restlessness, depression, delusions, possibly visual hallucinations, agitation, ideas of negation and stuporous condition preceding death. Orientation was fairly well preserved till the last few days. Physical examination showed cardiac hypertrophy and arteriosclerosis. (A full report of this case in J. of N. and M. D., 1908, 300.)

Anatomical Diagnosis.

Hypostatic pneumonia.
Hydropericardium.
Cardiac hypertrophy.
Atheroma of aorta; slight in basal vessels.
Mitral sclerosis.
Chronic localized fibrous peritonitis.
Slight fatty degeneration of liver.
Edema of pia mater.
Chronic sulcal and sylvian leptomeningitis.

Autopsy.—*The cause of death was pneumonia.*

The brain weighed 1445 grams. The pia contained considerable fluid and was milky over the vessels. The large blood vessels at the base showed some yellow atheromatous patches of irregular distribution; the lumina of the arteries was not diminished. The choroid plexuses showed a few minute cysts. There were no focal areas of softening in the brain.

Microscopic Examination.

From the fuller account of Southard and Mitchell, the following may be taken for the purpose of the present correlation:

Perivascular cell pigmentation everywhere marked.

Neuroglia cell pigmentation tends to affect the intermediate layers of the cortex.

Nerve cell pigmentation of the larger elements (Betz, solitary cells of Meynert) apt to be present, but present in the smaller elements, notably in the larger external pyramids of the frontal regions.

Nissl preparations showed an essentially normal layering.

Case 20 is that of a single man, a shoe-worker, who began to worry at 41, came to the hospital at 45 and died fifteen months later.

A bright, steady man, he took no medicine and was never sick until he failed in business.

At this time he began to worry and felt so badly that he went to the almshouse. For the next four years he did not improve, and before his admission to the hospital he expressed ideas of persecution and reference. Here he writhed and groaned throughout the physical examination; his extremities were blue, his movements feeble and groping; his knee-jerks greatly increased. In a few days he began to sit in one place, crooning, showing many stereotyped mannerisms, paying no attention to his surroundings. During his stay in the hospital he uttered words only once and then, a month before his death, asked an unimportant question.

Anatomical Diagnosis.

Pulmonary tuberculosis.
Bronchopneumonia.
Congested diploe.
Slight adhesive pleuritis.
Emaciation.
Decubitus.
(Liver weight 880 grams.)
(Arterial system seems normal.)

Autopsy.—*Cause of death was pulmonary tuberculosis.*

The calvarium weighed 410 grams, the brain 1400, each hemisphere 555 grams, and the brain stem 280. The pia was clear and delicate, the basal vessels free of gross changes. The cerebral substance was of soft consistency (8½ hours post mortem).

Microscopic Examination.

Perivascular cell pigmentation marked everywhere, but less marked than *neuroglia cell pigmentation.* Nerve cell pigmentation more varied than either; especially the *left precentral* gyrus shows some larger elements loaded with large granules, others practically without pigment.

Case 21 is a man who had his first manic attack at 44 or 47, going to a Connecticut hospital for six months, then coming here. He was violent; "could perform miracles." In five months he recovered and went home. At 62 he was again admitted, after four months of irritability, talkativeness, headache and at times confusion. For the next eight years he was euphoric—a chronic manic case.

Autopsy.—*The cause of death was dysentery.*

The brain weighed 1360 grams. The pia was thin; the convolutions full, showing no atrophies. The ventricles were smooth. The larger cerebral vessels showed no changes.

Anatomical Diagnosis.

Ileocolitis.
Ulcers of ileum and colon.
Slight sclerosis of coronary arteries.
Chronic apical pleuritis.
Chronic perihepatitis.
Cholelithiasis.
Chronic cholecystitis.
Hæmatoma of right ear.
Chronic pachymeningitis.
Chronic fibrous endocarditis.
Gaping sulci (precentral).

Microscopic Examination.

Perivascular cell pigmentation everywhere marked and almost uniform.

Neuroglia cell pigmentation marked or excessive.

Nerve cell pigmentation considerable to excessive (excessive in Betz cells, precentral).

Nissl pictures show subpial gliosis general and a suggestion of suprastellate pyramidal cell losses (frontal).

Case 22 is a divorced man in whom mental symptoms first appeared at 41, who entered Worcester hospital at that time and this hospital at 46, dying nine months later. (The age at death may have been 51, which would carry the onset forward to 45.)

His father was alcoholic and died insane; his mother was nervous; a sister is insane. The patient was a bright boy, never strong; he married at 27, had two children, was divorced because of his alcoholic habits. At 38 he was very irritable.

At 41 he talked to himself; lost his way in a familiar city. At the hospital he admitted auditory hallucinations, a strange feeling in the back of his head; later became voluble, over-active, said that people were following and talking about him. After ten months he seemed normal and was discharged. He supported himself as a cook. At 46 he began "to ramble about religion; he said that every time he mentioned the name of God he was stricken blind and could not open his eyes until inspired by a good thought. Here he never was known to answer a question directly. He would stop his walking and close his eyes queerly, or blink them, when asked for explanation." "You shouldn't ask a crazy man, he isn't supposed to know." "I lost my eyesight completely." Other replies—"They say I live in Lynn." "They say my father's name was Thomas Jefferson, but I can't help that." "Insane never keep track of the days, a thousand years in my sight is but a day." Always giving the impression of a strange exhilaration, probably well oriented, punning, rhyming, working well, often pacing the hall with peculiar swings and steps, he was five feet six inches in height, abdominous, weight 300. Four months after admission came an attack of jaundice which cleared in another month. In thirty-four days it reappeared, with tenderness over the gall-bladder, vomiting, collapse, dyspnœa, death.

Autopsy.—*The cause of death was acute cholecystitis.*

The brain weighed 1320 grams. It was firm; the convolutions well rounded.

Anatomical Diagnosis.

Abscesses of liver.
Acute cholecystitis.
Cholelithiasis.
Perforation of gall-bladder.
Acute peritonitis.

Jaundice.
Fatty infiltration and degeneration of pancreas.
Fatty liver (4940 grams).
Cirrhosis of spleen (640 grams).
Cirrhosis of kidney and pancreas.
Chronic nephritis.
Chronic aortic and pulmonary endocarditis.
Anthracosis of bronchial lymphnodes.
Lipoma of back.
Obese.

Microscopic Examination.

Perivascular cell pigmentation in general slight (considerable right superior frontal).

Neuroglia cell pigmentation considerable except precentrals and left frontal.

Nerve cell pigmentation marked in larger external pyramids of precentrals, elsewhere less (slight, calcarines).

Case 23 is a married man[6] who first became insane at 45, came to this hospital at 57 and died five months later.

A laborer of an ordinary sort. An uncle and a distant cousin were insane.

At 45 he began to think that fellow employees were mesmerizing him; he refused his pay because it had poison on it; voices told him to kill someone. At 56 he was still suspicious and very restless; there were two occasions when he had "sinking spells" for two or three weeks. On entrance he showed a dry skin, acne, pulse of poor volume, albuminuria, tremor, weakness, pupils slightly irregular and reacting poorly to light and accommodation; varicocele. Peripheral sclerosis was not marked; there was no speech defect. He was disoriented, irritable, slightly euphoric. He showed poor memory and some fabrication. In twelve days he became stuporous, paid no attention to pin pricks, had a temperature of 102; showed a tendency to cerea. Ten days later, still in bed, he said that God gave him the power to speak; "something comes over me and I can't talk—it's mesmerism." He complained of pain in head and arm, hallucinations. In another month he became weak and mute. He showed the signs of a pneumothorax.

Autopsy.—*The cause of death was bronchopneumonia.*

The pia, slightly opaque along the vessels, is considerably distended with clear fluid. The surface of the brain shows slight narrowing associated with very slight puckering of the frontal convolutions.

Localized bronchopneumonia with abscess formation.
Atelectasis of right lung.
Emaciation.
Slight generally distributed arteriosclerosis.
Chronic fibrous pleuritis.

Old scar of left lung.
Tricuspid insufficiency (relative).
Chronic diffuse nephritis.
Slight pachymeningitis.

Microscopic Examinatlon.

From L. B. Alford's description and a re-examination from the point of view of the present correlation, the following may be stated:

Perivascular cell pigmentation moderate.

Neuroglia cell pigmentation everywhere uniform and moderate.

Nerve cell pigmentation moderate and somewhat variable (*e. g.*, some large external pyramids of precentral regions show no pigment, others much).

Nissl pictures show occasional nerve cells markedly affected by satelletosis, but most nerve cells are intact. Frontal gliosis (white matter).

Case 24 is that of a man who began to act queerly at 46, who came to the hospital at 58 and died a year later.

A brother disappeared. A steady worker, quiet and good-natured, a weaver.

Somewhere in the forties he began to think that he could get gold out of stones; that moving picture companies had something to do with his stomach, making films from his feces to use against him. He could read secret symbols. On admission a tremendous hernia extended into the left scrotum; the same ideas occupied his mind; he had auditory hallucinations; he was well oriented and his emotional tone was normal.

Autopsy.—*The cause of death was intestinal obstruction.*

The brain weighed 1415 grams. The temporal lobes are softer than the rest of the brain. On the left side is a slight atrophy of the frontal region and flattening of the gyri in the motor region; these conditions are not so marked on the right. On section a cyst 4 mm. in diameter was found in the white matter of the left parietal region.

Anatomical Diagnosis.

Left inguinal hernia.
Bloody ascites.
Mesenteric lymphnoditis.
Congestion of lungs.
Chronic diffuse nephritis.
Valvular endocarditis.
Hypertrophy of heart.
Chronic fibrous myocarditis.
Interstitial fibrous splenitis.
Chronic perisplenitis.
Atheroma, general.
Chronic pachymeningitis.

Microscopic Examination.

Perivascular cell pigmentation moderate to slight.
Neuroglia cell pigmentation moderate, uniform.
Nerve cell pigmentation everywhere slight.

Case 25 is a man who became insane at 46, entering the hospital a month after the onset and dying three months after.

There was a negative family history. The patient had been a student at Harvard and successful at business and politics. At 24 he had a syphilitic iritis. He married at 41; had no children. At 44 he suffered from pain in his head and jaw and all his teeth were extracted.

A month before his admission at 46 he was unconscious for twenty-four hours and then very dull with intervals of brightness. He said that he "was dead and could not eat"; if he drank milk "someone else got it." On admission the pupils were irregular, unequal, with a slight reaction to light. There was tremor; reflexes were not disturbed. He was probably oriented. "I ain't a live man." "My leg is nothing but bone." "You can hit my leg with a hammer and not hurt me." "I have no pulse—no name." He was indifferent, irritable; finally had to be tube-fed. Wassermann in the blood serum strongly positive.

The cause of death was *bronchopneumonia,* possibly related to an acute *ulcerative gastritis.* There was an *acute renal degeneration* on the basis of *a chronic interstitial nephritis. Aortic,* slight *coronary* and slight *basal cerebral arteriosclerosis.*

Among chronic lesions were *endocarditis, splenitis, peresplenitis, perihepatitis, pleuritis.* Slight *hydrothorax* and *pericardium splanchnoptosis. Trochanteric decubitus. Emaciation.*

The brain weighed 1410 grams (Tigges' formula yields 1448 grams for subject 181 cm. long). The dura was adherent on the left side (frontal) and on right side (temporal and occipital—see remarks on inequality of hemispheres *infra*). Sulcal leptomeningitis along vessels (vertex, frontal, along longitudinal fissure).

Brain consistence increased, "doughy," especially prefrontal and precentral.

Cervical spinal dura thickened (cf. Wassermann serum positive). Spinal gliosis (no evidence of degeneration by Weigert method unless faintly in the cervical Goll).

The most striking feature of the brain is the *inequality of the hemispheres,* the left being longer than the right by about 1 cm. in greatest antero-posterior diameter. The *shortening* of the right hemisphere appears to be chiefly at the expense of the polar tissues and more particularly of the *frontal* polar tissue. The *occipital* polar regions differ in that the left pole is more tapering, whereas the *right pole* seems *compressed* forwards and downwards to yield an impression of greater bluntness and a tendency to the formation of a flattened posterior surface instead of a conical pole. There is, along with this shortening, little or *no evidence of distortion,* and bilateral symmetry prevails everywhere except in the polar convolutions. The convolutions of the under surface of the right frontal region fail to show definite signs of compression or redistribution of tissue; but on the other hand, the lower contour of the right temporal region suggests by a well-defined bulge (toward the posterior end of the third temporal convolution) that the tissues of this region have been antero-posteriorly compressed between the anterior face of the middle cerebral fossa and that hollow of the occipital bone which receives the occipital lobes. Unfortunately no exact data as to either the capacity or—what would be more important—a bilateral volume-comparison between the two middle fossæ are available.

A study of interior conditions yields some pertinent data. Thus the ventricles, wherever they appear in coronal sections, have not the same shape on the two sides, and posteriorly the *right ventricle* is appreciably *smaller than the left.* This condition strengthens still further the idea of right-sided compression which the brain may have undergone at some remote and probably very early date.

Moreover a study of the color-contrasts, grey and white, as revealed by photograph seems to indicate that the grey-producing elements must be less in evidence in the right superior, middle, and inferior frontal convolutions than in their left-sided fellows. This whitening-out of right frontal grey matter is best marked far forward (prefrontal region) and not at all marked in the orbital convolutions. A similar less well marked differentiation between right and left affects a coronal section taken through the occipital tissues: here especially appears to suffer a convolution inferior to the calcarine fissure.

The anterior ascending Sylvian branches are marked on both sides, and these so-called *intermediate precentral areas* give a certain impression of poor development (or, what seems less likely, atrophy) on both sides.

The corpus callosum has a good area of cross-section, but there is nevertheless a moderate thinning anterior to the splenium.

Microscopic Examination.

Little or no pigment in any of the cell types.

V. Clinical Summary.

SEX.

There are 15 female and 10 male cases in this series. The greater proportion of depressed cases, the association with the menopause, the occurrence of symptoms referable to the thyroid, tend to make of the women a more united group.

Heredity.

The family histories of three cases are unknown (8, 14, 15). Those of six cases (1, 5, 10, 20, 24, 25) are good.

In two cases (6, 11) a cousin is insane; in three (17, 12, 13) an uncle or aunt; in one (23) both an uncle and a cousin.

In five cases (7, 9, 16, 19, 21) a father or mother is insane; in three cases (2, 4, 18) a brother or sister; in one case (22) both a father and a sister; in another (3) both a mother and a brother.

In three cases, then, we know nothing of the hereditary factors; in six cases they are good; in 16 insanity appears in other members of the family and in 10 of these it appears in the parents or brothers or sisters.

Hereditary factors appear in 74 per cent of the cases with adequate history.

ANTECEDENT FACTORS.

The menopause was present at the onset of the first mental attack in seven of the fifteen women, and probably in one other case. In two or three more instances onset came within a year after the menopause. In two cases (9 a depression and 13 an excitement) onset preceded the menopause. Uterine cancer preceded the mental symptoms in one of the remaining cases and in the other we have no data.

In two cases extreme adiposity was associated with the onset of mental disease—in a woman with myxedema (15) and in a man (22) with pancreatic lesion.

As might be expected in the personalities of a group which has reached the forties without breakdown, only one is described as seclusive and peculiar (14, probably dementia præcox) while of those described 14 out of 16 are regarded as " normal, cheerful, sociable."

In trying to find how much arteriosclerosis was present near the onset of the psychoses we have used the history, the physical examination and the autopsy report—the last item losing its value as the age at death draws away from the age at onset.

Our group, from which the post-apoplectic cases had been ruled out, showed few evidences of early arteriosclerosis. Case 10 gave some clinical signs of arterial disease at 50 which autopsy at 52 failed to substantiate; so with cases 11 and 20. Three men (16, 17, 18) showed arteriosclerosis clinically and anatomically which probably dated back to the onset. Another man (19), generally sclerotic, showed neither the mental nor microscopical pictures which usually are associated. Case 25 began with a curious stupor (catatonic or apoplectic) and at autopsy arterial change was very slight.

Enlarged or abnormally functioning heart was noticed in six cases near the onset (7, 8, 10, 15, 18, 19). In two (4, 9) indigestion was regarded as an upsetting factor. Onset followed a cancer in case 5, hernia in case 24, a severe burn in case 3. One woman (4) had been deformed from infancy.

Cases 6 and 10 apparently broke down under unusually heavy domestic burdens.

Alcohol was prominent in the histories of two men (16, 22).

GENERAL CLINICAL FEATURES.

As the shortest way to bring the summary of disease courses to mind we present the following table of ages at onset, subsequent attacks, and death.

TABLE II.—AGE AT ONSET, SUBSEQUENT ATTACKS, AND DEATH.

Case.	Sex.	Age at			Duration of	
		Onset.	Subsequent attacks.	Death.	Attacks.	Life after onset of first attack.
1	F	48	52–56–65	65	5 years	17 years
2	F	42	Continuous	50	8 years	8 years
3	F	50	73	73	10 months	24 years
4	F	47	50	67	17 years	20 years
5	F	42	Continuous	42	7 weeks	7 weeks
6	F	44	Continuous	46	18 months	18 months
7	F	46	46–58	59	10 years	13 years
8	F	49	Continuous	62	11 years	11 years
9	F	46	Continuous	46	6 months	6 months
10	F	50	50–51	52	14 months	2 years
11	F	44	Continuous	48	4 years	4 years
12	F	47	One a year?	75	many years	28 years
13	F	43	Many, 8	68	many years	25 years
14	F	45	3 times a yr. for 11 yrs.	56	5 years?	11 years
15	F	44	Continuous	48	3 years	3 years
16	M	47	47–50	50	2 yrs. 9 mo.	3 years
17	M	45	Continuous	46	19 months	19 months
18	M	43	Remissions	46	3 years	3 years
19	M	49	Continuous	49	5 months	5 months
20	M	41	Continuous	47	5 years	5 years
21	M	44	44–47–62	70	9 years	26 years
22	M	41	41–46	47	2 years?	6 years
23	M	45	Continnous	57	12 years	12 years
24	M	46	Continuous	59	13 years	13 years
25	M	46?	Continuous	46	4 months?	4 months?

Attacks with recovery characterize six persons (1, 3, 12, 13, 21, 22).

Remissions characterize six cases (4, 7, 10, 14, 16, 18).

Continuous progress was observed in thirteen instances (2, 5, 6, 8, 9, 11, 15, 17, 19, 20, 23, 24, 25).

The longest continuous courses, 12 and 13 years, were in paranoid men. The durations of the others in order were: 11 years, 8, 5, 4, 3, 1.5, 1.5 years, 6, 4, 4 months, 7 weeks.

The most striking difference in durations of disease and life appeared in case 3, who in 24 years was ill 10 months.

Delusions characterized all the patients except one (15). The most prominent group is the somatopsychic, which appears in fourteen of the records (3, 4, 5, 6, 7, 9, 10, 11, 17, 18, 19, 22, 24, 25). Delusions of persecution are found in six cases, those in women having a sexual tinge (6, 7, 14, 20, 23, 24); allopsychic delusions appear also in seven other instances (2, 3, 9, 11, 19, 24, 25). Self-accusatory ideas appear in ten (1, 2, 3, 4, 6, 9, 11, 12, 16, 17); grandiose ideas in four (2, 4, 13, 21); ideas of self-unreality in two (19, 25); a total of 14 patients in whom autopsychic delusions are obvious. Delusions of negation appear in five (2, 3, 17, 19, 25) and of unreality in four cases (6, 11, 19, 25).

With reference to the somatic delusions, especially those of hypochondriacal sort, it is interesting to note that the actual physical conditions were rather worse (with allowance for obvious absurdities) than the patients' complaints would lead one to believe. Apparently the patient is apt to be nearer the truth than the observer who sees many superficial inconsistencies in his tale of woe.

Signs of *dysthyroidism* appeared in 4 cases. Cases 1, 2 and 14 showed exophthalmus with high pulse rate. Case 2 showed tremor also. Case 15 showed myxedema, obesity. Case 22 showed obesity with pancreatic lesion.

Apprehensiveness is a marked feature of ten cases (1, 2, 3, 6, 8, 9, 12, 18, 19, 20).

Hallucinations are shown definitely in 14 cases, and probably in 3 more, out of the 25 under consideration. The auditory type in thirteen (1, 2, 7, 8, 9, 11, 12, 13, 16, 18, 22, 23, 24); the visual in six (8, 11, 12, 13, 16, 18), always combined with auditory; the olfactory type in one (14).

Memory defect was brought out in only two instances (1, 23, 7?) and then late in the disease, at the ages of 56 and 65.

Orientation was good in almost every case; in two only was it partially disturbed in the early course of the disease (14, 15).

Diagnosis.

We hesitate to fit a diagnosis, according to the classifications now in vogue, to these disease forms, and we recall the sentence of Kraepelin to the effect that the field of the presenile psychoses is to-day the darkest in all psychiatry.

Our attempt gives us the following result:

TABLE III.

Case 1. A manic-depressive condition complicated finally by arteriosclerosis.
Case 2. A manic-depressive depression with involutional coloring.
Case 3. Two attacks of manic-depressive depression.
Case 4. Manic-depressive depression.
Case 5. Symptomatic depression.
Case 6. Manic-depressive depression with involutional coloring.
Case 7. Arteriosclerotic dementia.
Case 8. (Apprehensive excitement with dementia.)
Case 9. Manic-depressive depression of the involutional type.
Case 10. Manic depressive depression.
Case 11. Presenile psychosis.
Case 12. Manic-depressive; both phases.
Case 13. Manic-depressive manic with dementia.
Case 14. Dementia præcox?
Case 15. Myxedematous insanity.
Case 16. Manic-depressive; both phases.
Case 17. Manic-depressive depression with arteriosclerosis.
Case 18. Arteriosclerotic dementia, depressed state.
Case 19. Manic-depressive depressed (Cotard).
Case 20. Presenile psychosis with catatonic features.
Case 21. Manic-depressive manic.
Case 22. Manic-depressive mixed.
Case 23. Presenile psychosis with catatonic features.
Case 24. Dementia præcox.
Case 25. Manic-depressive depressed.

The diagnosis of a manic-depressive condition, then, is indicated in 15 of these cases, while three seem to fall under the heading of presenile psychosis, and only two under arteriosclerotic dementia.

If in a series of 124 cases arising in the forties, with the returns from gross and microscopical post-mortem examinations to help, we can find only 11 cases (2+9 in the post-apoplectic group) which deserve to be called arteriosclerotic dementia, this diagnosis is one to be very guardedly made by the clinician.

VI. Anatomical Summary.

Placing our cases in order of age at death we naturally find a general increase of arteriosclerosis with age. Comparing the ruled-out group of post-apoplectic cases, we may claim that our group has been lightly touched by arterial disease. Of the 13 cases over 50 the basal cerebral vessels were free of gross change in 7 instances.

The following table of brain weights shows 7 female cases underweight, one over; 3 male cases overweight, none under.

TABLE IV.—BRAIN WEIGHTS.

Case.	Age at death.	Brain weight.	Tigges' formula.	Case.	Age at death.	Brain weight.	Tigges' formula.
4	67	1040	1184 —	12	75	1310	1264 +
8	62	1085	1160 —	22	47	1320	1312
6	46	1105	1304 —	21	70	1360	1344
13	68	1105	1280 —	17	46	1395	1344 +
10	52	1155	1240 —	25	46	1410	1448
3	73	1195	1304 —	20	46	1410	....
1	66	1200	1216	24	59	1415	1384
5	42	1240	1248	19	49	1445	....
14	56	1245	1216	16	50	1450	1368 +
9	46	1260	1216 —	18	46	1475	1248 +
11	48	1310	....	....	....	....	....

Tigges' formula (height in centimeters x 8) is used as a ready means of obtaining the expected weight of the normal brain.

The distribution of pigment through the brain cells can be shown roughly in tables, if we represent no pigment by 0, slight by +, moderate by ++, marked by +++, and an extreme amount by ++++. It is often necessary to indicate two degrees of pigmentation in the same area, and to mark *var* those areas where there was marked variability in the pigmentation of the cells throughout one field.

TABLE V.—PIGMENT DISTRIBUTION.

Case.	Duration of life after onset.	Perivascular cells.	Glia cells.	Nerve cells.
5	7 weeks	o	o (+ occip)	o
25	4 months	o	o	o
19	5 months	+++	+++	+++
9	6 months	+	+++ (except g. rect.)	o
6	18 months	+	++ to +	+
17	19 months	+ (++ precent)	++ or +++	+ (++ precent)
10	2 years	o	o (+ occip)	o
18	3 years	o	++	+++
16	3 years	o	+	+
15	3 years	+++ (o precent)	+++	+++
11	4 years	+ var	+ to +++	o to +++
20	5 years	+++	++++	+++ var
22	6 years	++	++	++ var
2	8 years	++ to +	++ to +	+ to ++
14	11 years	++	++	++
8	11 years	+++	+++	+++
23	12 years	++	++	++ var
7	13 years	+++	+++	+++
24	13 years	++ to +	++	+
1	17 years	+++	+++	+++
4	20 years	o	++	+++
13	23 years	+	+	+
3	24 years	+	+ (+++ occip)	+
21	26 years	+++	+++	+++
12	28 years	+++	+++	+++

If we contrast Cases 21, 3 and 12, dying at 70, 73, and 75 years respectively with Cases 5 (dying at 42) and five others, 20, 9, 6, 18, 17 (all dead at 46), we find that all three septuagenarians show pigment in the three loci, whereas those who died at 42 (one case) and at 46 (6 cases) show as a rule (5 cases) little or no pigment in the perivascular and nerve cell loci but somewhat marked variations in amount in the neuroglia cell locus (2 cases negligible amounts). It must be remarked that one of the septuagenarians showed very slight amounts of pigment in any locus (except calcarine neuroglia), and this case (3) was precisely a case in which, although 24 years had elapsed since the first attack, the patient had been mentally normal in the interval. In contrast with this, we may mention 20, with maximal pigment in most loci (especially neuroglia; nerve cell locus variable in amount); this case had cyanosis of extremities and phthisis.

TABLE VI.

Case No.	Age at death.	Perivascular cells.	Glia cells.	Nerve cells.
5	42	0	0 (+ occip)	0
6	46	+	++ — +	+
9	46	+	+++ (except g. rect.)	0
17	46	+ (++ precent)	++ or +++	+ (++ precent)
18	46	0	++	+++
25	46	0	0	0
20	47	+++	++++	+++ var
22	47	++	++	++ var
11	48	+ var	+ — +++	0 — +++
15	48	+++ (0 precent)	+++	+++
19	49	+++	+++	+++
2	50	++ — +	++ — +	+ — ++
16	50	++ (+++ precent)	+	0
10	52	0	0 (+ occip)	0
14	56	++	++	++
23	57	++	++	++ var
7	59	+++	+++	+++
24	59	++ — +	++	+
8	62	+++	+++	+++
1	65	+++	+++	+++
4	67	0	++	+++
13	68	+	+	+
21	70	+++	+++	+++
3	73	+	+ (+++ occip)	+
12	75	+++	+++	+++

The Relation of Arteriosclerosis to Fifth Decade Insanities.

We may repeat for the fifth decade what was asserted for the sixth and seventh decades, " There seems to be no good ground for asserting that arteriosclerosis runs parallel with these insanities or has much more than a complicating relation to them." We except Cases 7 (?), 8 (?), 11 (?), 18.

Our case 3 is a good commentary on this assertion; psychosis at 50, health for 24 years, psychosis at 73, with a clinically and anatomically well-marked sclerosis which, we infer, developed without any corresponding mental change.

Correlations with Senile Atrophy.

The weight of the heaviest female brain is less than that of the lightest male. Seven of the female brains are underweight by Tigges' formula: none of the male brains is underweight. Duration of disease does not run parallel to the weight variations. On the average, however, the duration of life after onset was 11 years in the women, 7 in the men; this offers a rough correlation, not very satisfactory in view of the fact that the oldest man and the oldest woman had overweight brains.

Relations to Disorders of Internal Secretion.

The menopause was found closely associated with onset in most of the women; while this is to be expected, it is not less important because obvious. That lack of thyroid secretion should apparently cause the psychosis in one case, and increased secretion appear in three cases a year or more after onset, is surprising in a group of 15 women chosen as these were.

Relation of Fifth Decade Insanities to Dementia Præcox, to Manic Depressive Psychoses and Involutional Melancholia.

One may well hesitate to make a diagnosis of dementia præcox in any of this group. There seems to be little doubt in the case of a man with foolish paranoid ideas and lack of affect (24). The catatonic symptoms in three other cases (23, 20, 14) we may regard, as Kraepelin now suggests, as having only a superficial resemblance to the symptoms of the earlier decades.

The traits of the manic depressive psychoses, however, are seen everywhere in this group, and form a most tantalizing problem. We can say, without taking much for granted, that case 3, with its widely separated depressions, and case 21, with its distinct manic attacks, are pure cases (old recurrent melancholia and mania). We can imagine little objection to saying that five other cases are essentially manic-depressive but complicated by mental symptoms associated with arteriosclerotic (1, 13, 12, 17) and senile (4) changes. It is hardly worth while to consider manic-depressive insanity as applicable to the myxedema case (15), the paranoid woman (14), or the case classed above as dementia præcox. This leaves us with 15 cases, all of them liberally sprinkled with manic-depressive traits, all of them incomplete forms, almost all presenting facts hard to reconcile with any diagnosis. A strange group, selected because of its lack of certain characteristics, yet in some degree possessing common features—depressed, but with more cause than usual for the depression, clear, not sclerotic, not atrophic, showing striking but not uniform evidence of disturbance of internal secretions, and great variability in the outcome.

Starting this study with only a method, and no theory to prove or attack, it seems to us that the result has been to drive into the open a curious set of cases (an involution group) and make evident a further line of attack, a similar study of the decade just below them.

Summary and Conclusions.

1. We have reviewed a group of 25 cases of mental disease (Danvers State Hospital material), so selected as to offer a fair sample of mental diseases arising in the fifth decade of life.

2. Our principle of selection excluded all cases which were obviously *not* characteristic of the fifth decade (paresis, alcoholic mental disease, and the like); the group of non-characteristic cases thus excluded was extremely large (approaching 80 per cent of all cases arising in the decade) and the preventable diseases alone amounted to over 60 per cent.

3. We remained with a group of 25 cases (10 males and 15 females) which present certain common aspects. These cases may be *negatively* defined as *not* due to syphilis, alcohol, cerebral arteriosclerosis, brain atrophy, or other factors yielding coarse brain disorder; as not possessing pronounced schizophrenic features; as not uniform in course or outcome; as not likely to show either elation or expansive delusions. They may be positively defined as almost, if not quite, constantly subject to delusions at some stage in each case; as yielding manic-depressive traits in the large majority of cases; as prone to depressive features; as possessing a strong hereditary taint (74 per cent of properly studied cases); as not infrequently suggesting disorder of glands of internal secretion.

4. The delusional features, present in all cases (save one of myxedema), were not characteristically of any particular form; the delusions were somatic in 14 cases; dealt with various alterations of personality in 14 cases (combined with somatic delusions

in 8 instances); and (superficially at least) dealt with the social environment in 13 cases (6 times combined with other forms).

5. As to somatic delusions, it is further of note that a physical basis could be recognized for many of them in diseases of the viscera; and that, on the whole, these visceral counterparts of the delusions were more serious than the patients' complaints themselves.

6. Delusions of negation (5 instances) and of unreality (4 cases) do not bulk so large statistically as they are apt to in descriptions of so-called involution-melancholia.

7. The group, taken as a whole, is far more suggestive of manic-depressive insanity than of dementia præcox or of any other form of mental disease.

8. On the whole, depression is the most common manic-depressive feature of these cases: but the constant occurrence of various delusions alongside the depressive emotions makes the latter seem far from "causeless," certainly not so causeless-looking as the depressions of manic-depressive insanity.

9. It cannot be dogmatically asserted; but, on the whole, these patients seem more dominated by various ideas and by various more or less false beliefs than are the manic-depressives of earlier decades, and are perhaps more victims of intellectual than of emotional or volitional disorder. However, this may be more appearance than reality, and further work may again pull the emotions, and particularly the depressive emotions, into the genetic foreground.

10. As to the designation "involution-melancholia" for these cases, it may be surmised that the term was adopted by alienists having *unpleasant delusions* at least as much in mind as *unpleasant* MERE *emotions.* Perhaps it is unwise to seek to overthrow the classical term before more intensive work has been done on the actual relation of the intellect to the emotions in this group: how far then, it may be asked, is the melancholia of involution merely systomatic and responsive to intellectual conditions?

11. Since Freud has claimed a sexual basis for paranoia and even perhaps for paranoic states falling short of paranoia, it is fair to inquire how far the present group has a sexual basis: three of the fifteen female cases in our series harbored rather systematic delusions of persecution, and all three systems had a sexual tinge.

This fact, allocated with the not infrequent tendency to disorder of glands of internal secretion in certain cases, ought to provide a fruitful field for psychoanalytic hypotheses.

12. Hallucinations, as a rule auditory, were observed in something like 60 per cent to 70 per cent of the cases: there are *à priori* reasons (Wernicke) for relating these with the unpleasant delusions characteristic of the group; but, whether the false beliefs irradiate over to incite the hallucinations, or whether the hallucinosis is a prime factor in producing the false beliefs, must remain an open question: statistically we should be forced to favor the former process.

13. The post mortem data throw some light on the negative definition of our group (see paragraph 3 supra). There appears to be little or no evidence that the metabolic disorder, if there be such underlying this group, tends to brain wasting.

14. Our study of the distribution of certain chemically ill-defined lipoids (or pigments, as we have called them) shows that age plays some part in the amount of deposits, perhaps more in the neuroglia cells than in the nerve-cells, and least of all in the perivascular phagocytes.

15. All cases living three years or more after onset of symptoms show more or less marked accumulations of pigment in neuroglia cells; the same cases show a greater variability in the nerve-cell accumulations; occasionally such a three-year or over-three-years case will show a negligible amount of pigment in perivascular phagocytes.

16. These pigment-findings are in substantial agreement with those of Southard-Mitchell, 1908:

(a) "Perivascular cell pigmentation almost uniform in different areas of the same case." The present series presents only two instances of marked variability from area to area.

(b) "Neuroglia cell pigmentation * * * varies more or less directly with age." Our present group presents more variation than did the former; there is however no absolutely negative case over 46 years of age.

(c) "Nerve-cell pigmentation is not a function of age." Two cases of 50 years or more showed no appreciable amount of pigment, and three others showed but slight amounts. The variations in amount within a given brain are more striking than the variations shown by the neuroglia cell pigments.

17. That these three loci for the deposition of pigment tend at last to a species of saturation is indicated by the fact that the *even* degrees of moderate or of marked pigment deposit in all loci begin to appear in the later years of life (one case at 49 years, one at 56, and the rest from 59 to 75 years).

18. The fresh point of view thus obtained for the problem of involution-melancholia by our study of fifth-decade insanities may be stated as follows:

Involution-melancholia has been regarded as possibly akin to manic-depressive insanity or even identical therewith or as possibly something quite different. Perhaps the majority of psychiatrists would regard it as a disease akin to manic-depressive insanity but modified by climacteric or presenile changes and distinguished from manic-depressive insanity by the peculiar tendency to depression which has given it its name. The novel feature of our investigation has been to study the age-factor. We have studied unselected cases arising in the fifth decade of life, excluding all coarse organic cases of brain lesion. Our resultant group is, we believe, although small, otherwise ideally representative of the conditions underlying mental disease at this age-level. Our group includes a sufficient number of the familiar cases of involution-melancholia as well as cases of delusional insanity without melancholia. The striking fact is that the *melancholia cases* prove also *delusional*. In so far as our group is representative of the fifth decade, we believe that the essential *psychopathia involutionis* is characterized by delusions, that in the large majority of cases melancholia is a feature superadded to the delusions, and that in a smaller majority of cases hallucinosis also occurs. The fact that melancholia may assert itself as the most prominent symptom in the clinical foreground fails to controvert the possible genetic importance of the delusions. As to the cause of *psychopathia involutionis*, it is easy to invoke the glands of internal secretion; and of their disorder there is actually some sign in a number of cases. Whether such disorder or some unknown factor determines the over-pigmentation (lipoid accumulations) in the cortex above noted, and whether these deposits have a direct relation to the symptoms must rest with the future.

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XXXII

HOW FAR IS THE ENVIRONMENT RESPONSIBLE FOR DELUSIONS?[1]

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THE analysis of somatic delusions, that is, of false beliefs concerning the body or organs of the patient, shows (if our Danvers autopsy material yields a fair sampling) that there is a strong peripheral element therein.[2] The correlations which we can make with more or less facility between somatic lesions and somatic delusions suggest that the process of somatic delusion-formation is rather one of elaboration than of manufacture. Even the somatic delusions of general paresis itself may often be shown to be correlated with lesions of the soma; and, where the soma is negative, still the damaged brains of these paretics are likely to show a spread of lesions back of the Rolandic fissure in various sensory-elaborative areas, or even in the optic thalamus at a still more external plane in the centripetal path of sensory impulses.[3] The evidence from normal brain cases and from paretics, where careful correlations are executed between the particular delusions felt and the possible organic sources of these, leads one almost irresistibly to the conception of a strong, sensational, perceptual, or, in some cases, hallucinatory origin for the somatic delusions in question.

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[1] Being Danvers State Hospital Contributions Number 38, 1913. A portion of the expense of this work has been borne by the Investigation Fund of the State Board of Insanity, Massachusetts.

[2] E. E. Southard. On the Somatic Sources of Somatic Delusions. Journal of Abnormal Psychology. VII, 5, 1912–1913.

[3] E. E. Southard, assisted by A. S. Tepper. The Possible Correlation between Delusions and Cortex Lesions in General Paresis. To be published in the next number of The Journal of Abnormal Psychology, which is the August-September, 1913, issue.

Can a parallel hypothesis be erected for those delusions which primarily concern or seemingly concern the environment, whether social or not social? If the soma and its parts are often found to provide significant material for delusions concerning the soma, can we suppose that the environment, and especially the social environment, will likewise be found to provide the significant features of those delusions termed, in Wernicke's nomenclature, *allopsychic?* Can we invoke the perversity of inanimate objects to explain the misfit of various persons in their environment? Can we admit that the interests of the *Alter* are so by nature opposed to those of the *Ego*, that granting a tendency to delusions or to what may be termed the *paranoid capacity*, one social environment is bound to show sufficient cause for delusions touching said environment?

It seemed proper so to entitle our former considerations (On the Somatic Sources of Somatic Delusions) that the reader might surmise a close parallelism between source and content of delusions. Was it proper to suppose that titles like "*the environmental* (*or social*) *sources of environmental* (*or social*) *delusions*" and "*the personal sources of delusions concerning the personality*" would adequately cover the results of investigation in the allopsychic and autopsychic fields respectively?

Simple as such a one-to-one correspondence of cotent and source might appear, there were several reasons why the proof could not be easy.

In the first place, it is obviously not so easy to draw the line accurately between the self and the environment. Although all might agree that the self and the environment could be theoretically and practically distinguished in broad strokes, it is clear that the concept of personality is still obscure to many theorists and that the delimitation of the self is practically a matter of doubt (witness James' celebrated chapter on the Consciousness of Self).

The practical doubt as to what constitutes an allopsychic as opposed to an autopsychic delusion early appeared in the present investigation. We started, as in the analysis of somatic delusions, by choosing "normal-brain" cases, *i.e.*, cases in which the anatomist at the autopsy table failed to discover lesions of consequence in the brain, in a series of one thousand cases.

Cases without gross destructive lesions	306
Cases *listed as* showing allopsychic delusions	117
Cases *listed as* showing allopsychic delusions *only*	58

But further investigation showed that among these fifty-eight cases listed as allopsychic only, fourteen cases had to be excluded because the beliefs expressed could not be safely stated to be delusional. That is to say, medical revision of a lay classification of recorded beliefs had to exclude almost nineteen per cent of these beliefs (or statements in the histories taken to mean beliefs) from the delusional group. This error of almost one in five is the more surprising when one considers that the lay workers occupied with the original classification resorted to physicians constantly in matters of doubt, to such an extent that no one doubted that the classification would be found fairly representative of the records.

We then excluded a further group of cases because the personal histories were absent or so meager as to forbid any sort of correlation between beliefs and the patient's environment, leaving us finally with a group of thirty-one cases of allopsychic delusions for analysis.

CLINICAL AND ANATOMICAL NOTES (CONDENSED)

CASE I (D.S.H., 6,497, Path. 477): "*Acute melancholia*," feared "*could never go home*;" was "*going to be buried alive.*" The patient was an unmarried Irish-Catholic rubber-worker, whose mother and sisters had died of tuberculosis and, as an incident apparently in her own attack of phthisis, became hyper-religious ("*a great sinner*"), called for the priest, and finally in the hospital became quite mute.

Death from extensive bilateral tuberculosis of lungs (chronic and acute), ulcerative tuberculous enteritis with ascites, emaciation and anasarca, and ovarian atrophy.

Case II, (D.S.H. 7,095, Path. 503): "*Acute melancholia*," was "*to be punished for something she had done*," and had a "*sister who told lies about her.*" Patient was an unmarried Catholic house-maid of ordinary mental capacity who turned from a cheerful person into a melancholic one for a period of three months, recovered, and became depressed again. Much headache. In hospital, much *praying with beads.*

Like Case I, Case II died of extensive bilateral tuberculosis of lungs (including right pyopneumothorax) and showed some abdominal lesions (ascites, cholelithiasis). Subperitoneal fibromyoma of uterus.

If not so essentially autopsychic as Case I, it would seem that Case II would hardly fit a strictly allopsychic group.

Case III (D.S.H., 9,678, Path. 653): A catatonic dementia præcox patient, a married Baptist woman, born in New Brunswick, although she appeared to move in a world of spirits. "*Everybody is a spirit but our body is dead*," had a well-developed autopsychic center ("*bad girl*").

This case likewise had extensive bilateral tuberculosis of lungs as well as abdominal and pelvic lesions (tubercles of ileum and cecum, eroded cervix uteri).

Case IV (D.S.H., 4,588, Path. 272): A lumber dealer in business difficulties. "*Afraid something dreadful is to happen to family*," "*folks have died.*"

Lesions: Enlarged prostate, diverticulum of bladder, pyelonephritis. Aortic and aortic valvular sclerosis.

Case V (D.S.H., 1,434, Path. 280): Alcoholic Irish gardener of sixty-six years. "*Everyone trying to injure him*"; "*annoyed by witches*" (swore at witches for years); "*large property in China.*" Cardiac (aortic insufficiency, mitral stenosis, hypertrophy); large chronic gastric ulcer; chronic peritonitis with adhesions. There is some doubt whether the brain was normal in this old case (granular ependymitis of fourth ventricle, chronic leptomeningitis).

Case VI (D.S.H., 5,933, Path. 331): Woolen manufacturer, seventy years, occasionally blue, occasionally alcoholic, slight shock a year before admission. "*People plotting and trying to rob him,*" "*officers after him,*" "*moved money from bank to bank,*" "*may be burned up,*" "*family all dead.*" Emaciation, abscess of leg, aortic sclerosis, basal cerebral arteriosclerosis, chronic leptromeningitis.

Case VII (D.S.H., 12,340, Path. 978): Unmarried school-teacher, manic-depressive, developed delusions ("*people hypnotizing her,*" "*other people filthy*"; patient "*had cancer,*" made "*poor investments*" in western lands (delusion?).

Patient's brother drunkard. Previous attacks showed alternately depression and excitement. The delusion "*had cancer*" was thought to be not a genuine somatic delusion.

Chronic lesion: chronic diffuse nephritis.

Death from septic mitral endocarditis and pneumococcus meningitis.

Case VIII (D.S.H., 11,538, Path, 993): Housewife of a worrying and hypochondriacal type, amnesic at fifty-seven, had delusions. "*People trying to poison her,*" "*to be killed and cut up in pieces,*" "*other patients telling immoral stories*" (delusion?).

Lesions: Fatty liver, fatty heart, hemorrhages in skin, emaciation.

Case IX (D.S.H., 13,364, Path. 1,115): An unmarried shoeworker, given to worry and to dislike of children, home life unpleasant, hypomaniac at fourteen (patient at Danvers), again at twenty-eight. *Delusions:* "*People trying to injure her,*" "*people talking to hurt reputation,*" "*to be poisoned.*"

Lesions: Malnutrition and chronic dermatitis. Slight mitral and parietal endocarditis, Scars of apices. Chronic gastritis, chronic adhesive cholecystitis, chronic periappendicitis, hydrosalpinx. Dilatation of thoracic aorta. Granular ependymitis of fourth ventricle.

Case X (D.S.H., 3,252, Path. 151): Diagnosticated "*acute maniacal chorea,*" was a waitress of somewhat alcoholic and irregular life ("*fear of pregnancy*") (delusion?), excited, suicidal. "*People trying to get father's money,*" "*parents would be turned out of house because patient was in Danvers.*" Hallucinations (people talking through ventilators).

Lesions: Pregnancy, ten weeks. Partial placenta prævia, slightly fatty liver. Death from pneumonia.

Case XI (D.S.H., 11,394, Path. 821): Very possibly a manic-depressive case (third attack at sixty-three years after exhaustion by nursing cancerous husband). Despite delusions of "*control by an Indian doctor*" and of "*going to be killed*" or "*etherized,*" "*confined,*" had a considerable coloring by autopsychic factors ("*will never get well,*" "*calls self an Indian*").

The chronic lesions in this case were chiefly abdominal and pelvic (hypernephroma of kidney, chronic diffuse nephritis, fibromyoma and polyp of uterus) although the chronic passive congestion of liver was associated with cardiac disease (including coronary sclerosis).

Case XII (D.S.H., 5,970, Path. 346): Carpenter of fifty-four years, diagnosticated general paresis, history of syphilis. *Delusion:* "*Some one or some animal trying to get at him.*"

Lesions: The autopsy showed instead of paresis large areas of chronic internal hemorrhagic pachymeningitis with organization over frontal, parietal and part of occipital regions. Contracture of legs, slightly aortic sclerosis, slight chronic adhesive pleuritis, decubitus, emaciation.

Case XIII (D.S.H., 7,094, Path. 372): Housewife, with insane uncle and cousin; for some years distrustful of husband (would not trust him with bank book), "shock" eighteen months before admission, at sixty-five. *Delusion:* "*Clothes being taken away,*" patient suffering *bad treatment.*

Lesions: The case perhaps hardly belongs in the normal-brain group by reason of marked cerebral arteriosclerosis and marked chronic fibrous leptomeningitis. However, no special lesions of the brain were noted. Cirrhosis of the liver, cholelithiasis, chronic diffuse nephritis, aortic sclerosis and aortic valvular sclerosis with calcification.

Case XIV (D.S.H., 8,349, Path. 486): Swedish housewife, married; originally of a cheerful disposition, had mental symptoms at the menopause at fifty-one and a second attack with sleeplessness at sixty-two. *Delusion:* Patient said "*neighbors stole flowers*"; patient was "*undergoing electric shocks.*"

Lesions: Cause of death pneumonia; chronic lesions, chronic obliterative pleuritis of both sides, bronchiectases of right upper lobe, mitral valvular sclerosis, chronic interstitial nephritis, chronic gastritis, numerous fibromyomata of uterus.

Case XV (D.S.H., 367, Path. 526): Married Irish housewife, probably manic-depressive. History of domestic trouble, attack at thirty-six (Worcester State Hospital), and at thirty-eight. Death at forty. Delusions of infidelity of husband and as to husband's attempting to get money to spend for other women (delusions?).

Lesions: Hypertrophy and dilatation of heart, chronic passive congestion of liver. Cholelithiasis, chronic interstitial nephritis. The thick and eburnated calvarium frontal osteitis, chronic external adhesive pachymeningitis, a slight degree of chronic leptomeningitis and sclerosis of the arteries at the base of the brain, with a brain weight of one thousand one hundred grams, suggest that the brain was not entirely normal, but since no lesions of the cortex are recorded, the case has been put in the "normal-brain" group. There is considerable question whether this case showed true delusions, and there is some evidence that the beliefs concerning patient's husband were at least partially grounded.

Case XVI (D.S.H., 856, Path. 854): Unmarried Irish Catholic servant-maid of low mentality, and always eccentric character, had delusions that people were "*stealing from her*," and that people "*talked about*" *her.*

The autopsy indicates that it would hardly be safe to describe the brain of this imbecile as normal, since it weighed one thousand and thirty-five grams, and showed chronic internal hydrocephalis, with marked cerebral arteriosclerosis, and chronic external adhesive pachymeningitis. There was mitral sclerosis, cardiac hypertrophy and a moderate degree of coronary arteriosclerosis, the liver was slightly fatty; there were subperitoneal fibromyomata of uterus.

Case XVII (D.S.H., 8,463, Path. 600): Swedish epileptic laborer (traumatic injury of skull, two operations with partial relief); despondency. *Delusion:* "*Followed by animal intending to devour him.*"

Lesions: Of a chronic nature, included hypertrophy and dilatation of heart, chronic passive congestion of liver, chronic perisplenitis, and bilateral chronic obliterative pleuritis. There were ecchymoses of the fundus of the stomach and tuberculous ulcers of the ileum. Cause of death, bilateral phthisis.

Case XVIII (D.S.H., 10,352, Path. 687): A laborer, formerly of cheerful though reserved disposition, at seventy-five years became irritable and irrational, talked to himself, and became vagrant. Failed to recognize his family, became restless and noisy, struggled and shouted "*murder.*" *Delusions:* "*Family down on him*" and "*wants to get rid of him.*"

Lesions: Chronic interstitial nephritis, slight coronary arteriosclerosis, death from hypostatic pneumonia.

Case XIX (D.S.H., 7,690, Path. 717): Housewife of reserved disposition, stated to be "unkind and mean at home, though agreeable and entertaining to strangers"; stated to have put arsenic in beans and to have poisoned daughter. Obscene and violent and sometimes homicidal. Death at seventy-five. *Delusion:* Transient, "*every one was going to steal from her.*"

Chronic lesions: chronic diffuse nephritis, cholelithiasis, left-sided chronic obliterative pleuritis, adhesions of right lung, vegetative tricuspid endocarditis.

Case XX (D.S.H., 10,923, Path. 756): German woman of seventy-four years, with amnesia for ten years, noisiness at night for two years, disorientation for place and time. *Delusion:* "*People come to the house at night to steal.*"

Lesions: Cholelithiasis, abscess of gall bladder, and occlusion of cystic ducts, chronic nephritis. The brain weight, nine hundred and twenty-five grams, indicates very probably that this case should be put in the group of senile atrophic dementia.

Case XXI (D.S.H., 1,093, Path. 760): A carpenter, naturally of a melancholy and reserved disposition, said to have suffered congestion of the brain twenty-five years before death, at sixty-six; had mental symptoms for a period of three months, at sixty-two. *Delusion:* "*Wife and daughter are keeping patient at hospital in order to spend his money.*"

Lesions: Prostate enlarged, heart hypertrophied, kidneys contracted, sclerosis of aorta with calcification, moderate mitral sclerosis, and fibrous endocarditis, cataract of right eye. Death from pneumonia, arteries at the base of the brain were sclerotic and there was diffuse chronic leptomeningitis. The brain, however, weighed one thousand four hundred and fifty grams.

Case XXII (D.S.H., 10,787, Path. 769): Widowed butcher of sixty-seven years; cheerful, occasionally alcoholic to excess. In the forties was quite wealthy but fell into business troubles, failed at sixty-five, has become worried and melancholy since. *Delusion: "Something he ought to tell but couldn't"; "was put in asylum to get property"; "to be killed and poisoned"; "all food poisoned"; "was defending himself in a breach of promise suit."*

Lesions: Death from pneumonia; chronic lesions, emaciation, mitral sclerosis and chronic adhesive pleuritis. Arteries at base of brain were sclerotic.

Case XXIII (D.S.H., 10,783, Path. 775): Blind, disoriented housewife of eighty-four years; melancholy after death of daughter. *"People had ill-treated her." "If she walked about she would walk on children."* Threw food about for children.

Lesions: Cardiac, arteriosclerotic, cholelithiasis, old appendicitis. Cerebellar cyst of softening would tend to exclude case from the normal-brain series. Chronic internal hemorrhagic pachymeningitis.

Case XXIV (D.S.H., 9,975, Path. 778): An imbecile gardener, forty years, brooded over lawyer's letter for weeks. *"Everybody down on him," "people chasing him and trying to kill him"; "to be taken away and killed."*

Lesions: Extensive tuberculosis, probably pulmonary in origin, but extending to peritoneum, lymph nodes, liver.

Case XXV (D.S.H., 11,140, Path. 780): Once successful shoe manufacturer, eighty-one years, of good character and ability; latterly suspicious, confused, sleepless, restless.

Delusions: "Patterns stolen."

Lesions: Cardiac, arteriosclerotic. Chronic nephritis was the only abdominal lesion. The brain was beyond question atrophic, as well as arteriosclerotic at the base.

Case XXVI (D.S.H., 11,147, Path. 812): Somewhat inferior grocer who failed in business and became stubborn, irritable and full of *ideas of persecution* by wife and her family (delusion?). Syphilis at twenty-five. Immoral.

Lesions: Pernicious anemia with posterior column sclerosis. Cardiac, arteriosclerotic. Abdominal lesions few, (chronic perisplenitis, slightly fatty kidneys).

Case XXVII (D.S.H., 11,804, Path. 865): Died at seventy-one after two years of increasing dementia. *Delusions: Apprehensive; "House broken into," "brother-in-law to blame."*

Lesions: Death from pneumonia. Cardiac disease, with chronic passive congestion of liver. Chronic interstital nephritis.

Case XXVIII (D.S.H., 3,702, Path. 939): Catholic housewife, two commitments at thirty-one and thirty-four, childbirth assigned cause. *Delusions:* Jealous and suspicious of husband; "*others filthy,*" "*divine authority,*" "*toilet filthy.*"

Lesions: Cardiac disease and complications. Arteriosclerosis.

Case XXIX (D.S.H., 6,373, Path. 1,032): Alcoholic Irishwoman, forty years. "*People call her bad names.*"

Lesions: Death from pulmonary tuberculosis. Disseminated tuberculosis of both lungs. Miliary tuberculosis of liver and left kidney. Thrombosis of iliac and femoral vein. Atrophy of left leg. Chronic external pachymeningitis, slight edema of *pia mater*, chronic adhesive pleuritis, atrophy of right optic nerve.

Case XXX (D.S.H., 13,011, Path. 1,056): Unhappy Irish housewife. *Delusions:* Complicated delirium due to streptococcus meningitis. *Food and water poisoned.*

Case XXXI (D.S.H., 7,280, Path. 689): An imbecile servant-maid, alcoholic, from an alcoholic family; fifty-two years.

Delusions: Persecution. Persistent thymus, thyroids small, brain atrophic. Ascites, ovarian atrophy.

Analysis of these thirty-one cases shows at least eight cases with a well-marked alteration of the personality recognized by the patient. All but one (a case, [V, 280] not certainly equipped with a normal brain, who alongside unpleasant yearlong delusions of *injury by witches* sometimes mentioned *property in China*) showed delusions of an unpleasant nature only. On one (Case X, 151) the *fear of pregnancy* was grounded in fact, and the case should perhaps, be counted out of our group either as non-delusional or as somatopsychic. Another (Case XXIII, 775) felt an apprehension about *walking on children*, somewhat reasonable in view of her impairment of vision, (nor is it clear whether her ideas of *ill-treatment by others* were delusional).

It would perhaps be going too far to call these eight cases essentially non-allopsychic just because they exhibit autopsychic changes. Nevertheless we are inclined to think that in Cases I (477), II (503), and possibly III (653), the delusion-formation spread, as it were, outwards from a conceived alteration of the Ego rather than inwards from a conceived alteration of society. That is to say, we should regard the delusions of these cases as essentially egocentrifugal rather than egocentripetal from the patient's point of view. Case V (280) 's late delusion of grandeur may possibly have been of brain-manufacture, and, so far as it goes, is of an egocentrifugal character from the patient's viewpoint. Case X (151) was, if delusional, in the same group. Also Case XXIII (775).

On the other hand the autopsychic delusions complicating Cases VII (978) and especially XI (821), seem to be of an egocentripetal character as viewed by the patient. That is, these two cases of predominantly allopsychic content remain essentially allopsychic even after their autopsychic complications are reviewed. The selves of these patients are, as it were, damaged by a spreading inwards of the delusion-formation (egocentripetal from the patient's point of view and possibly from the outsider's point of view).

From this sketchy analysis of certain impure cases of allopsychic delusion-formation, we accordingly obtain a method of approach in the analysis of various mixed cases which we have so far not analyzed.

We will proceed to consider the remaining group of twenty-three cases in which no certain traces of autopsychic or somatopsychic change can be found. There, if anywhere in this material, shall we be able to determine what share the environment may have had in actually producing (from the outsider's point of view) the delusions which concern the environment.

We at once find three *imbeciles*, Cases XVI (854), XXIV (778), XXXI (689), from whom it is hard to exclude the effects of personal abnormality from any analysis of their reactions to the environment. (Possibly Case XXV [812] belongs also in this group.) In these cases we may surmise that, however little the patients may themselves have suspected it, there were being wrought in their lives certain, as it were, egocentrifugal effects, egocentrifugal, that is to say, from the alienist's point of view.

Faults of temperament are recorded in another series of four cases (VIII [993], IX [1,115], XIX [717], XXI [760]), which again argue that not the environment alone was responsible for the allopsychic delusions, but that the delusions were in some sense (though perhaps hidden from the patients) egocentrifugal in origin. Again, there is a group in which the effects are possibly due to, or complicated by, organic brain disease (of such a nature as to elude the diagnostic forms dealing with the *cortex cerebri*, but of sufficiently definite nature), Cases XII (346), extensive organized internal hemorrhagic pachymeningitis; XVII (600), epileptic with cranial trauma; XXX (1,056), streptoccocus meningitis. It is of interest to note that the delusions in XII and XVII resembled each other ("*some one or some animal trying to get at him*" and "*followed by animal intending to devour him.*")

We remain with thirteen cases in which to prove our hypothesis that environmental difficulties might account for delusions of an allopsychic nature. Of these, eight (Cases XIII [272], XIV [486], XVIII [687], XX [756], XXV [780], XXVII [865], XXVIII [939], XXIX [1032]) exhibit little or nothing environmental to account for their delusions. Brain-manufacture or cortical injury to the personality might be urged in the arteriosclerotic Case XIII, the senile atrophic Case XX, the arteriosclerotic and atrophic Case XXV.

We remain with six cases in which environmental causes seem to stand in fairly close connection with the delusions. Business difficulties here stand first (Cases IV

XXXIII

CONTRIBUTIONS TO THE NEUROLOGY OF THE CHILD. I.

BY W. P. LUCAS AND E. E. SOUTHARD.

There is an unnecessary gap in our knowledge of nervous diseases in children, due to the lack of co-operation in the recording of data between the hospitals for acute disease in children and the institutions for chronic conditions. On *a priori* grounds it seemed to the writers that there might be a relation between acute disease of the nervous system and subsequently developing epilepsy or feeble-mindedness, a relation obscured by lack of inquiry into subsequent histories on the part of the children's hospitals and by lack of knowledge in the institutions for chronic and defective conditions concerning the medical data on file in the children's hospitals.

In particular, despite the silence of books on epilepsy concerning encephalitis as a basis for persistent convulsive tendencies, there seemed *a priori* reason to suspect such a relation. In the first place, it is highly probable that *certain epilepsies acquired by adults are grounded in encephalitis.* A case published by one of the writers in another connection in 1908[1] will perhaps bear repetition in abstract:

Case of acquired epilepsy in a fisherman of sixty-eight years, fatal in nine weeks: Focal acute encephalitis of right cornu ammonis.

The patient, a fisherman, born in 1836, had a number of insane but, so far as could be learned, no epileptic relatives. Scarlet fever in childhood had left him slightly deaf. There were two accidents with unconsciousness, one a fall from mast-head at fifty-four or fifty-five years with unconsciousness three or four hours; the other at sixty-five, unconsciousness from vapor on a launch. A gradual decay of faculties began at sixty-six years: failure of memory, depressive ideas, train of thought limited to fishing, attacks of trembling without unconsciousness, irritableness. At sixty-eight years, nine weeks before death, the patient began to have fits which were at first severe but infrequent (three, once with a slight shock, in the first three weeks), then grew less frequent, but remained severe, and ended by four days of practically continuous convulsions with unconsciousness (over four hundred attacks). The convulsions were general, clonic, with head and eyes turned to left, right arm flexed over abdomen, thumb drawn under fingers, left hand extended by side. At times there were tonic convulsions.

The autopsy (four hours after death) showed the following conditions:

Intracranial congestion. *Focal encephalitis of right cornu ammonis.* Bronchopneumonia of hypostatic distribution. Coronary arteriosclerosis with calcification. Aortic and renal arteriosclerosis. Chronic valvular endocarditis. Chronic fibrous myocarditis. Fatty myocarditis. Chronic passive congestion of liver and kidneys. Marked chronic external adhesive pachymeningitis.

Following is a description of findings in the head: *Calvarium* not notable. *Dura mater* completely and firmly adherent to calvarium. *Sinuses* negative. Arachnoidal *villi* moderately developed. *Pia mater* dark in color, with veins intensely engorged. Pia mater a little hazy and in the frontal regions distended with liquid. None of the intracranial *arteries* show macroscopic signs of arteriosclerosis. Weight of encephalon, 1,270 gm. Blood content of cortex high. There are no notable anomalies in size or arrangement of gyri. The gyri are as firm as normal except that the cornua ammonis are a little firmer than usual. Section of the encephalon in various parts shows intense injection of the brain substance affecting both gray and white matter. The right cornu ammonis shows a grayish-red linear streak running about the convolutions in the nerve-cell layers. This has an anteroposterior extent of perhaps 1 cm.

Such a case, however, fails to prove conclusively that *subsequent to recovery from* an acute encephalitis or other *nervous disease*, i. e., *after an interval without convulsions*, there may set in one or more *periods of convulsions* to be ascribed to some residual condition of the tissues. Such a possibility in the adult is indicated by the data of a case also published by one of the writers,[2] a *case of cornu ammonis epilepsy*, due, not to encephalitis, but *to aneurysm of the left anterior choroid artery*. In this case, which died in confirmed epilepsy at the age of sixty, there has very fortunately been a connection between general hospital and insane hospital data which demonstrates that the first convulsion occurred at the age of forty-four, and very probably due to the beginning of the aneurysm's effects upon the surrounding tissues, either by local hemorrhage or pressure.

Neither of these adult cases is so convincing as would be a properly recorded case of epilepsy developing in childhood or youth, with adequate medical data concerning the early history. In undertaking an analysis of appropriate cases at the Children's Hospital, Boston, and attempting to see the recovered cases and learn the institutional fate of some, we have been confronted with the *lack of precision in diagnosis* in the field of encephalitis.

The diagnosis of encephalitis has not been made with precision until recent years, either by internists or by neurologists. In fact, it was no earlier than 1884[3] that Strümpell first offered, as an hypothesis, the conception of infantile cortical hemiplegia as due to encephalitis. The great pandemic of influenza in 1889–90 called definite attention to brain inflammations of bacterial origin, and in 1893, from the surgical side, the brilliant work of Macewen on "Pyogenic Diseases of the Brain and Spinal Cord" may be said to have established these possibilities firmly in the medical mind. In 1895 the influenzal origin of one group of cases was established by Nauwerck.[4] In 1904, the pyogenic origin was established of a classical example of the Strümpell type, a case of cortical hemorrhages following scarlet fever in a boy of five years (Southard and Sims[5]). And a further study by Southard and Keene[6] of five more cases, one a girl of twelve and the others adult, appeared to warrant the conception that there is a group of cases of acute hemorrhagic encephalitis due to the staphylococcus pyogenes aureus. In addition to the influenzal and pyogenic types, it is probable that another type occurs due to some cause identical with or similar to the cause of anterior poliomyelitis. But that determination rests with the future.

This review suffices to show that, if the diagnosis of encephalitis has not been habitually rendered either in private or in hospital practice until of late years, the reason is founded on the uncertainty or unclearness of our conceptions of encephalitis.

In investigating cases at the Children's Hospital, Boston, we have been aided by the fact that for some years past Dr. W. N. Bullard, of the Children's Hospital consultant staff, has taken much interest in the subject and has rendered the diagnosis of encephalitis in certain cases. The results we bring are only a beginning, but we hope that as a consequence pediatric workers will work more consistently on such data and that the workers in epilepsy will procure as careful investigations as possible into the previous histories of their early cases, sending out messengers, if possible, to procure the details which practitioners carry in their note-books or in their minds and are habitually lost for any scientific purpose.

In order to visualize this condition it may be well to construct a *typical history* of onset and course of a pediatric case of acute encephalitis, and to illustrate the final outcome by a number of examples from our own cases: A child of five or six years while walking along the street suddenly falls dazed for no apparent reason. In falling he strikes his head but inflicts no injury. He is picked up and carried still dazed into the nearest house. There he has one or two convulsions that involve the right side more than the left. In an hour he has apparently regained consciousness sufficiently to inquire his whereabouts. He seems dull, speaks in a far-away manner, and on questioning him as to what has happened he is unable to answer coherently but begs to go home. On reaching home in the same semi-conscious condition he is put to bed and passes a very restless disturbed night. He seems feverish and even more listless and stupid than immediately following the initial attack. He complains of feeling nauseated, and on attempting to have him take a glass of milk, he vomits profusely. Following this he has another convulsion, and it is then noticed for the first time that his right eye is turned in, there is slight facial paralysis on this side as well as marked weakness of the right arm, but there is also some involvement of the left side, shown in the apparent hypersensitiveness of that side and of both lower extremities. His deep reflexes are variable, but on the whole exaggerated. Pupils are equal but sluggish to light reaction. Knee-jerks are very lively. Kernig is present at times, absent at other examinations. His temperature ranges from 100 to 105, his pulse is rapid and respirations moderately so. This general condition continues for a week or ten days, during which time he has from one to three convulsions a day. He is very sensitive to touch or sound, complaining loudly of pain on being examined, and crying out that his head ached if there was any excessive noise in his room. Towards the end of this time his temperature begins to drop and the convulsions are of a less severe type and of shorter duration. In two weeks he shows evidence of wanting to sit up, is markedly less stupid. There still remains a general muscular weakness, more noticeable on the right, and the paralysis of the external rectus still persists. If left alone, however, he spends most of the day in dozing and, if wakened suddenly, has noticeable general muscular twitchings. His appetite increases rapidly and at the end of three weeks he is up and about, apparently normal except for (*a*) ocular paralysis, (*b*) defective memory, (*c*) at times defective impressibility (familiar objects not recognized), (*d*) will disorder (" has to be coaxed " to do things), (*e*) confusion or bewilderment under conditions of excitement.

A few weeks later the mother reports with him, alarmed because on the previous evening he had had " a fit " lasting about three minutes, after which he had seemed dazed and had gone to sleep very shortly. In the morning, however, he seemed to be "himself." Examination showed simply the residual ocular paralysis and bewilderment on questioning.

The series we wish to present comprises twelve cases, all having been seen at the Children's Hospital within the past five years.

The onset in these cases was sudden. In 3 there was a speedy remission which was followed later (within five days) by the more definite group of symptoms. Convulsions appeared repeatedly in 7 out of the 12 cases; in 4 it was definitely noted as absent; and in the remaining case it was not noted in the history as either present or absent.

Rigidity of the neck is noted as present in 9 cases, and in the remaining 3 cases no note is made of this condition.

In 5 cases nausea with vomiting is mentioned, while in the remaining 7 cases no note is made as to the occurrence of vomiting.

In this series there were only 2 in which cerebration was not affected and was noted as normal while under observation; in these 2 cases, however, convulsions were present. In the remaining 10 cerebration was affected, from a slight mental retardation to prolonged unconsciousness and slow recovery of the normal mental processes.

Motor involvement is noted in every case, ocular paralysis being the most frequent, being present in 7 of the 12 cases. The eye-ground was, however, normal in all cases which were examined except a possible slight congestion of the retinal vessels in one case. Other motor involvements varied from weakness of the extremities to actual hemiplegia.

The reflexes were affected in all but 2 cases in which they were stated to be normal. Knee-jerks were absent in 3, lively in 1 and very variable in 6 cases. Kernig was definitely noted in only 3 cases, and in 2 of these the intensity varied considerably at different times.

The blood picture showed nothing beyond a moderate leucocytosis in every case (6) in which it was done, varying from 10,000 to 33,000+.

TWELVE CASES OF E HALITIS IN CHILDREN.

No.	Age.	Onset.	Convulsions.	Vomiting or Nausea.	Rigidity of Neck.	Cerebration.	Motor Involvements.	Reflexes.	mperature.	White Blood Count.	Spinal Fluid.	Duration of Acute Attack.	Complications.	Immediate Results.	Present Condition.
1	5 years	Sudden	General twitchings	Present	Head held to left	Normal	External strabismus on left	Normal	to 100	Not made	Not examined	14 days	None	Marked improvement, internal strabismus remained for 6 months	Normal boy
2	3 years	Sudden	Not noted	Not noted	Not noted	Unconscious	Right hemiplegia	Knee-jerks liv		Not made	Not examined	21 days	Scarlet fever, otitis media	Slow improvement, periodic convulsions	Convulsions increased, died during convulsions 21 months later
3	5 years	Sudden	Absent	Not noted	Not noted	Sluggish	Internal strabismus, aphasia, general weakness, difficulty in swallowing	Knee-jerks sent	to 100	19,700	10 ccm., clear, twenty cells per cubic millimeter, fibrin clot, all mononuclear cells	12 days	None	Improved	Normal
4	4 years	Sudden	Present	Present	Not noted	Psychomotor retardation	Right arm weak	Knee-jerks va able	to 102	28,000	Clear under pressure, all mononuclear cells	28 days	Varicella, otitis media	Improved slowly with occasional convulsion for 6 months	No convulsion for 1 year. Right internal strabismus remains moderate. Mentally normal.
5	5 years	Sudden	Present	Present	Present	Sluggish	Ptosis. General weakness. Facial paralysis	Knee-jerks un equal	to 100	18,000	Clear, no pressure	21 days	None	Improved slowly	Normal except he is nervous, easily mentally tired
6	3 years	Sudden	Present	Not noted	Present	Normal	Marked facial paralysis	Normal	to 103	Not made	Not examined	17 days	None	Marked improvement; few convulsions for 6 months; facial paralysis remains	Normal and healthy boy. Marked internal strabismus
7	3 years	Sudden	Present	Not noted	Present	Not noted	Weakness of legs	Knee-jerks ab sent. Pupil sluggish	to 103	Not made	Not examined	9 days	None	Improved very slowly. Frequent convulsions	Improving slowly at Hospital Cottages for Children
8	6 years	Sudden	Present	Present	Present	Unconscious	General	Suggestive Ke nig. Cloau Pupils dilated	to 103	33,600	Clear under pressure, no clot	17 days	None	Improved slowly. Mentally deficient	Physically normal. Mentally deficient. Occasional convulsions
9	5 years	Sudden	Absent	Not noted	Present	Semi-conscious	Strabismus. Legs weak. Loss of sphincter control	Kernigs variabl Pupils dilated	to 101	16,000	Clear under pressure, small clot, mononuclear cells	6 days	None	Improved rapidly. Slight strabismus for 6 months	Perfectly well. When tired slight tendency to strabismus
10	3 mos.	Sudden	Present	Not noted	Present	Normal	Paralysis of palate. Constant twitching	Knee-jerks varia ble. Pupils di lated, no r traction t light	to 104	Not made	Clear under pressure, no clot, few cells, all mononuclear	33 days	Otitis media	Died	No autopsy
11	3 years	Sudden	Absent	Not noted	Present	At times unconscious	Ocular	Knee-jerks ab sent		Not made	Clear under pressure, fine clot, 180 mononuclear cells to the cubic millimeter	7 days	None	Died	Autopsy
12	6½ years	Sudden	Absent	Present	Present	Dull, semi-comatose	Ptosis of right lid	Knee-jerks slug gish	to 104	12,000	Forty ccm., clear under pressure, no clot, all mononuclears	14 days	None	Improved rapidly	Apparently normal

The finding in the spinal fluids is of importance as this is very often the only point of differentiation between encephalitis and tubercular meningitis. The points of interest are that the fluid was usually under slight pressure, and that the amount withdrawn was not excessive except in one case, in which 40 ccm. was withdrawn. The fluid was clear in every case, and even on standing in only 1 case did a clot form and then only a very small clot appeared. Fibrin shreds were noted in 2 others, but in these 2 cases it was noted that no clot formed after having stood twenty-four hours.

The only complication noted as having occurred during the entire acute attack was otitis media, which appeared in 4 of the 12 cases. Clinically there was nothing to attach any importance to in the appearance of otitis media in these cases, though in subsequent study of the group the importance of early blood cultures in all such suspicious cases is strongly suggested to the writers as perhaps being of great value in showing in some cases an infection by known agents, as bacillus influenza, staphylococcus pyogenes aureus, pneumococcus. In other cases, the blood and cerebrospinal fluid will prove negative. The pyogenic instances are frequently incidents of the convalescence from exanthemata. Experience from adult cases of influenzal origin would indicate that a perfectly normal interval may follow an influenzal attack and only weeks later the signs of encephalitis ensue. For these matters see Oppenheim's book [7] or a more recent account by one of the writers in Osler's Modern Medicine.[8]

We give in detail *a case with subsequent epilepsy.*

Jan. 23, 1909. Children's Hospital. F. C., age three years.

Family history. — Father, mother and six children well and normal. No deaths, no miscarriages. An aunt is reported to be epileptic.

Past history. — Normal birth. Always well. In July, 1908 (when two and one-half years), had a convulsion for which she was given castor oil and dieted. Apparently made a speedy recovery and had been well from that time to onset of present trouble six months later.

Present illness. — On Jan. 20, 1909, taken sick suddenly, seemed "fretful and queer" and a few minutes later had a convulsion. Has had fifteen or twenty in three days. Has vomited once. Has been apathetic between convulsions but conscious. Has been feverish and constipated.

Physical examination. — She was a well developed and nourished child, very apathetic but conscious. Pupils were equal but reacted sluggishly to light. Knee-jerks could not be obtained. There was moderate rigidity of neck. There was a suggestive Kernig on the right. Spleen was not palpable. In every other way the child was normal. Her history while in the hospital was one of apparent rapid recovery. On entrance her temperature was 103°; this fell by lysis and on the ninth day was normal. Her white cell count was 23,000, taken the day after entrance. Her spinal fluid was negative. Skin tuberculin reaction was negative. She had no convulsion while in the hospital, and her mentality cleared up slowly, so that two weeks after her onset she seemed to be bright, sat up in bed and wanted to play. Knee-jerks were very slow in returning and were still very slight when she was discharged, twenty days after the onset. She was very weak on standing and seemed unable to balance herself.

She was discharged very much relieved and apparently normal on Feb. 7, 1909, or twenty days after her acute onset.

Subsequent history. — On writing to her parents for further information about her present condition it was learned that shortly after leaving the Children's

Hospital she had a return of convulsions and had been sent to the Hospital Cottages for Children at Baldwinville, Mass. Dr. H. W. Page, the superintendent of the Hospital Cottages for Children, was kind enough to furnish us with the following information: "F. C. at the time of her admission here rarely went more than three or four days without an attack. On the days on which the attacks occurred she usually had more than one, often three or four, and they were severe. During her stay here, there has been a marked lengthening of the interval between the attacks, and diminution in the severity of them. In the last three months, she has only had four slight attacks. This is certainly encouraging, but we have learned to be very cautious as to the ultimate outcome."

Another case which showed all the symptoms of *acute encephalitis* and which died with *subsequent autopsy* may be of interest.

C. S. was a healthy boy of three years of age. Father and mother were both perfectly well. There were several other children in the family, all well. There was no family history of any mental disease. Family was free of tuberculosis, and neither the father nor the mother were alcoholic. He had had none of the children's diseases. He was admitted to the hospital on the fifth day of illness, with the following history: Five days before, he had suddenly become very listless and feverish. He had not vomited, but had complained of pain in his head. At times he was unconscious. He had no convulsions. He had eaten practically nothing. The parents could not state whether he had been nauseated. When brought into the hospital he was in a semiunconscious condition, with marked right internal strabismus. His knee-jerks were absent and he was perfectly flaccid, except for the muscles of the neck, which were markedly rigid. His temperature on entrance was 102. His respirations were shallow. His general appearance was that of a tuberculous meningitis case and that was the clinical diagnosis which was made. His blood was not examined. Lumbar puncture showed clear fluid under slight pressure which formed a clot on standing and had 180 cells, all mononuclear, to the cubic millimeter. No tubercle bacilli were found. In less than forty-eight hours after admission he died. The clinical diagnosis of tuberculous meningitis had not been changed, notwithstanding the fact that no tubercle bacilli had been found after careful search. The following is the autopsy report:

Autopsy at the Children's Hospital, June, 1909, by Dr. L. J. Rhea. C. S., three years old, nine hours post mortem.

Body. — That of a well-developed, well-nourished male infant; skin dry and smooth; no external glandular enlargement; external orifices are normal. Rigor mortis present; slight lividity of dependent parts. Mucous membrane pale. Pupils 5 mm. and equal. Abdominal fat 1 cm. thick; firm and yellow. Muscles bright red.

Peritoneal cavity. — Normal. Lesser peritoneal cavity normal. Mesenteric lymph nodes slightly increased in size, moderately firm and bright red. Appendix, 9.5 cm.; retrocecal; mesentery short; no adhesions. Diaphragm: left fifth rib; right fourth interspace.

Pleural cavities. — Right normal. Left practically obliterated by dense, firm adhesions, most marked in the lateral, posterior aspect, especially the lower lobe. A portion of the upper lobe normally covers the pericardial cavity and is firmly bound to the latter by dense adhesions. Parietal pleura is removed intact.

Pericardial cavity. — Normal.

Heart. — Weight, 56 gm. Endocardium normal. Valves are normal. Right auricle slightly distended with fluid, blood and post-mortem clot. Foramen ovale closed. Coronaries normal. Measurements: Tricuspid valve, 7.0; mitral valve, 6.0; left ventricle, 0.7; pulmonic valve, 4.0; aortic valve, 4.0; right ventricle, 0.3 cm.

Lungs. — Right: crepitant throughout. Upper lobe salmon pink and dry; middle lobe not well defined, only anterior being distinct from the upper lobe; lower lobe dark red, crepitant throughout and on section fluid blood containing air escapes. Left: visceral pleura is covered with dense fibrous tags. The whole lung is dark red; deeper red in the lower lobe. The lung is crepitant throughout; but crepitation slightly decreased, especially throughout lower lobe posteriorly. Mediastinal and peribronchial lymph nodes very slightly increased in size and bright red.

Spleen. — Weight, 30 gm.; rather firm; dark red; malpighian bodies distinct; trabeculæ moderately distinct.

Liver. — Weight, 400 gm. Reaches 3 cm. below ensiform in the mammary line and extends just to the lower margin of the ribs. The surface is smooth; on section is of distinct yellowish color. Parenchyma rather friable. Gall bladder and ducts normal. Gall bladder contains small amount of thick, greenish bile.

Kidneys. — Weight, 100 gm. Capsule strips easily, leaving a smooth surface. Cortex averages 6 mm.; grayish-white. Malpighian bodies distinctly visible. Parenchyma extends slightly beyond the capsule. Pyramids are dark red. Pelves and ureters normal.

Adrenals. — Normal.

Pancreas. — Normal.

Gastro-intestinal tract. — Stomach is empty; mucous membrane is pale, lined with thick, mucoid material. This tract contains a small amount of fluid fecal material. Mucous membrane is normal. Peyer's patches and solitary follicles are not hypertrophied.

Aorta. — Normal.

Organs of the neck. — Thymus gland hypertrophied. The two lobes are distinctly separated. Lower border of the organ extends almost to the lower border of the pericardial cavity. With all adherent tissues removed, thymus gland weighs 31 gm. On section uniform pale gray in color and rather soft in consistency. Tonsils not hypertrophied. Tongue and pharynx, larynx and trachea are normal. Thyroid gland normal. The glands of the neck are distinctly palpable and very slightly increased in size; on section they are bright red.

Genitalia. — Normal.

Head. — Covered with a sparse growth of white hair.

The scalp strips easily from the calvarium; sutures closed; calvarium normal. The dura is adherent to the calvarium, most marked along the great longitudinal sinus. This sinus contains a small amount of post-mortem clot and fluid blood. Pacchionian granulations are normal in amount and distribution. The dura strips easily from the pia. The two halves of the brain are symmetrical. The blood vessels are slightly injected. The pia is smooth and glistening and the subpial vessels are slightly injected. The corresponding areas of the lateral hemispheres are similar in consistence. The basal vessels are normal. On section, the lateral hemispheres, cerebellum and basal ganglia show no gross lesions. The ventricles are smooth, glistening and contain a normal amount of straw-colored fluid. In the region about the olivary body, especially in its anterior half, the brain tissue is slightly brownish in color and slightly softer than normal. There is one small discrete yellowish area about 1 mm. in diameter; no other gross lesions are demonstrable. The meninges are free from exudate, moist and smooth. The sinuses at the base of the skull contain a small amount of post-mortem clot.

Spinal cord. — Shows no gross lesion.

Middle ears. — Normal.

Pituitary gland. — Normal.

Anatomical diagnosis. — Acute inferior encephalitis. Chronic adhesive pleuritis (left). General glandular enlargement. Thymus large.

Cross section of medulla at level of decussation shows acute myelencephalitis suggestive of appearance in the "poliomyelitis" group. There are accumulations of lymphocytes in the sheaths of the vessels in both white and gray matter, but as a rule more abundant in the gray matter and especially in the caput cornu ventralis.

In the region of the caput cornu ventralis, also, are the only appearances suggestive of recent neuroglia cell-proliferation.

The nerve cells of the gray nuclei show moderate acute changes, most marked (although here not severe) in the cells of the gracile nuclei, suggesting early axonal reaction (as if the appertaining fibers had been injured, possibly in their course through the fillet higher up in the medulla; this would be consistent with the situation of the soft brown region noted by Rhea in the gross).

There is everywhere a moderate subpial edema with a moderate though distinct lymphocytic infiltration (several plasma cells noted). The pial infiltration is at every point far less extensive than the infiltration of sheaths of vessels that approach the pia.

To exclude syphilis the microscopic picture is scarcely adequate, but vascular wall changes should be more in evidence and there should also be more evidence of gliosis.

That the case is one of very recent production is rendered probable by the lack of satellite cell proliferation about nerve cells.

Sections of spinal cord show characteristic poliomyelitis with a few hemorrhages superimposed upon the picture of nerve cell destruction, lymphocytosis and phagocytosis of vessel sheaths in gray matter, and acute neuroglia cell changes; the spinal meningitis is slightly more marked than the medullary meningitis.

Diagnosis: Poli-encephalitis.

CONCLUSIONS.

1. The records of the Children's Hospital from 1905 to date have been searched for possible instances of encephalitis. Cases of "encephalitis," "toxic encephalitis," "meningitis?," and "?, encephalitis?" have been considered.

2. Twelve cases have been chosen which may with some reservations be regarded as cases of encephalitis. These show onset always sudden.

Paralysis or paresis in all cases (oculomotor paralysis in 7). Deep reflexes altered in 10. Mental symptoms in 10. Rigidity of neck in 9. General convulsions, 7 (absent in 4). Nausea or vomiting, 5 (not noted in 7).

3. The results fall into three groups: (*a*) Death during acute attack, 2 cases (X and XI). (*b*) Recovery from acute attack, with subsequent epilepsy and mental deficiency, and death after twenty-one months, 1 case (II). (*c*) Recovery from acute attack, with residual symptoms, 5 cases (I, III, V, IX, XII); 2 normal, except for strabismus and possible slight mental change (IV, VI); 2 epileptic and mentally defective (VII and VIII).

4. With respect to epilepsy, the total incidence of convulsions during the acute attack was 7 in 12. Of 9 cases still living, 5 showed convulsions during the acute attacks, and 2 of the 5 (VII and VIII in chart) are epileptic.

5. In both epileptic cases there was a brief interval between recovery from the acute attack and the onset of epilepsy.

6. The detailed histories of a case developing epilepsy and of a fatal case with autopsy are presented.

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CONTRIBUTIONS TO THE NEUROLOGY OF THE CHILD: II NOTE ON THE MORTALITY AND THE PROPORTION OF BACKWARD CHILDREN IN CASES OF CONGENITAL SYPHILIS FOLLOWED SUBSEQUENT TO HOSPITAL TREATMENT.

THE IMPORTANCE OF SUCH AN INVESTIGATION.

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During the past few years our attention has been focused on the treatment and diagnosis of syphilis more than ever before, and it is a natural consequence that one should turn to a study of this disease in children.

The present study was taken up as a part of a much larger investigation, in which both treatment and diagnosis of congenital syphilis are to be considered. This particular portion deals entirely with the subsequent history of a series of cases which we were able to follow up in the desire to find out the previous condition of cases treated in previous years.

Out of several hundred cases which have been treated at the hospital and whose records were available, we were only able to trace about sixty cases. Many of these, as will be seen by the protocols, are too recent to judge what their final outcome will be.

The material naturally divided itself into three groups:

(1) THE ONES WHO APPARENTLY ARE MENTALLY NORMAL.

In this group there are nineteen, five of whom are of school age, ranging from six to sixteen years. All these received treatment for varying periods and at various times as stated in the protocols, but on examination they seem to be normal mentally.

There are ten cases of this class who are between two and six years of age, and it is considered rather hard to decide in these cases whether they were entirely normal or not, but in every case where there was any doubt we gave them the benefit of it. They were put through no special tests to determine their relative mentality. There were four below two years of age. It is hardly fair to judge the mentality of these, and in our percentages they will be left out,—only children of school age being considered.

(2) THE ONES WHO ARE BACKWARD MENTALLY.

In this group there are nineteen, eleven of school age, varying from six to sixteen years of age, and showing all grades of backwardness,—from those who are only slightly backward in their school grades to those who are under institutional care for feeblemindedness. There are eight between the ages of two and six. These show unmistakable signs of retardation mentally, and so can, without any question, be put into the second class of backward mental development.

(3) THE THIRD GROUP OF TWENTY-ONE ARE THOSE WHO HAVE BEEN FOUND TO HAVE DIED.

The investigation attempted to cover both the family history and the history of the individual child, whose record was in the hospital. This at times was found almost impossible as very often only meagre information could be obtained about the family and other children. All the living children were personally investigated and interrogated as much as allowed by the family. The children, however, were put through no special tests.

It is hoped that such a study can be carried out later, especially on the class of the mentally backward children.

Special emphasis was laid throughout the investigation on their mental condition, as it seemed to the writer that this is the most important thing in the future of any child: whether the child would be dependent or whether the child could, by its own intelligence, support itself.

The following histories of the various cases will show what this investigation has brought out in each case, as will also the chart in a rather more graphic and shorter way.

CASES MENTALLY NORMAL.

No. 7, three years, male.

History of Specific Infection. Snuffles was first noticed when a few days old. Skin eruption appeared when three months old. Treated for a few weeks with mercurial ointment until eruption disappeared.

Subsequent History. Has had no trouble since. His general health is very good. No signs of any specific trouble at present. Slight excess of general glandular enlargement. Mentally is apparently perfectly normal for a child three years of age. The family history, however, in this case shows that a brother now five years old is rather backward, with indistinct speech and rather hard of hearing. This, however, may be due to a double otitis media, which he has had for some time. Mother has been on specific treatment since 1906 off and on. She says she has had no miscarriages and no still-born children. Father has deserted the family.

Prognostic Outcome. In this case, it is too early to say whether this boy will be mentally normal or not; at least he has a brother who is not.

No. 10, six and a half years old, female.

History of Specific Infection. When five weeks old had typical skin eruption and snuffles, for which she received mercurial ointment, and these disappeared rapidly. She has had no trouble since except headaches at times.

Subsequent History. Goes to school in the second grade; standing is good and is considered bright.

No. 18, eleven years, male.

History of Specific Infection. When a few weeks old had typical eruption and snuffles, and was treated for a few weeks with mercurial ointment, when these disappeared. When four years old again came to hospital, complaining of headaches and general glandular enlargements. Was put on mercurial treatment again, under which he rapidly improved. He was under treatment for several months at this time, and has had no return since.

Subsequent History. General health seems now at eleven years apparently good. He is in the sixth grade at school, and his standing in his class is fair, and intelligence is counted medium.

No. 23, seven years, male.

History of Specific Infection. When a few weeks old had typical skin eruption and snuffles; for which he was treated with mercurial ointment. These disappeared very rapidly, and he has had no treatment since.

Subsequent History. General health is good. Child has not gone to school, but seems apparently normal mentally, though he is rather nervous.

No. 25, six years old, male.

History of Specific Infection. When four weeks old had typical skin eruption and snuffles; treated for several weeks with mercurial ointment, when these disappeared.

Subsequent History. When five years old, had severe headaches, for which he returned to the hospital, and was again put on mercurial treatment, under which these rapidly disappeared, when the child again discontinued treatment. At present, seems physically to be perfectly well. Mentally, he has not gone to school yet, but seems bright; apparently normal for a boy of six.

No. 26, fifteen years old, female.

History of Specific Infection. When an infant had typical snuffles and skin eruption for which she was treated with some ointment, under which these rapidly disappeared.

Subsequent History. Was not seen in hospital until age of ten, when she had typical pharyngeal ulcers, for which she was treated at hospital with mercurial ointment and mercury internally. These cleared up fairly rapidly; she has been in good health ever since. At fifteen years of age, she is in second grade of high school, standing apparently good, and she seems fairly bright. She wears glasses (astigmatism and slight cloudiness of disc in left eye), and is somewhat nervous.

Prognostic Outcome. Is good both from a physical and mental standpoint.

No. 29, four years, female.

History of Specific Infection. When three weeks old she developed typical skin eruption and snuffles. Symptoms disappeared under treatment rapidly. Has had no treatment since four months old.

Subsequent History. She seems at present perfectly normal physically and mentally for a child of four.

No. 30, four years, female.

History of Specific Infection. When four weeks old developed typical skin eruption and snuffles. Treated with mercurial ointment for a few weeks until these disappeared; has received no treatment since.

Subsequent History. At present, physical condition is fairly good. She has periostitis of her left tibia. No other signs of specific lesions. Mentally she seems bright; for a child of four she seems apparently normal.

No. 32, six and a half years, male.

History of Specific Infection. When a few weeks old had typical skin eruption and snuffles, had mercurial ointment treatment, which was kept up for a short period of several weeks. Has had treatment off and on since then.

Subsequent History. As skin is rough, he is subject to superficial ulcers. Is constantly under treatment. He also is subject to diarrhea, eight to ten stools a day, if not under treatment. Physically, he is not very strong; mentally, he seems to be of medium intelligence.

Prognostic Outcome. Fairly good mentally; probably poor from a physical standpoint. May be dependent on account of health or may be from early secondary involvement.

No. 33, four years, female.

History of Specific Infection. When six weeks old developed typical skin eruption and snuffles; was put on mercurial treatment and kept on this off and on for the first year and a half.

Subsequent History. She has been well since then. General condition and mentality seem perfectly normal at present for a child of four.

No. 35, four years, male.

History of Specific Infection. Shortly after birth, developed typical skin eruption and snuffles; was treated with mercurial ointment, under which everything cleared up very rapidly; has had no treatment since.

Subsequent History. Now at four years of age seems apparently normal except for a slight excess of glandular enlargements.

No. 40, three years, female.

History of Specific Infection. When five weeks of age, she developed typical skin eruption, condyloma, snuffles. These cleared up rapidly under mercurial ointment treatment.

Subsequent History. When two and one-half months old, considered well. Has had no treatment since. At present she seems apparently normal for a child three years of age.

No. 45, four years, female.

History of Specific Infection. When a few weeks old, snuffles and typical skin eruption appeared, for which she was treated with mercurial ointment a few weeks until the lesions disappeared.

Subsequent History. At one and one-half years old she had some sores on her chin, buttocks and genitalia, for which she was treated in the hospital with mercurial ointment. They rapidly cleared up under this treatment, and she had not reported again.

Present condition. Her general health is very good. She still has scars of the sores on her chin and body. Mentally, she appears moderately bright. She has not gone to school, but can talk fairly well for a child of four.

Prognostic Outcome. Rather early to judge what her mental capacity is going to be.

No. 50, one and one-half years, female.

History of Specific Infection. When a few weeks old developed a typical skin eruption and snuffles; was treated for a few weeks with mercury.

Subsequent History. Has had no treatment since three months of age. Present condition: She has an anal condyloma; otherwise no signs of specific condition. General health is good and as far as can be made out at this age her mentality is within normal limits. Facial expression is perfectly normal. However, at one and one-half years of age she has not walked.

Prognostic Outcome. Presumably within normal limits.

No. 51, fourteen months, female.

History of Specific Infection. When a few weeks old, developed typical skin eruptions and snuffles. Put on mercurial ointment; symptoms disappeared rapidly. Has not been treated since.

Apparently seems to be perfectly normal. Too early to judge mental condition.

No. 59, twenty-one months, female.

History of Specific Infection. When two weeks old had typical skin eruptions and snuffles, and given mercurial treatment.

Child seems apparently normal physically and mentally. Too young to judge of real condition.

No. 62, five years, female.

History of Specific Infection. When a few weeks old had typical skin eruptions and snuffles, and treated with mercurial ointment.

Subsequent History. Mother died shortly after birth; father deserted at this time. Child has been under State care, and they report that she is perfectly healthy and mentally apparently normal.

No. 64, four years, female.

History of Specific Infection. When a few weeks old, child had typical snuffles and skin eruption, and treated for a few weeks.

Subsequent History. Family moved out of town, and report from family is that she is perfectly normal both as to health and mentality.

No. 65, one and one-half years, female.

History of Specific Infection. When five weeks old had typical skin eruption and snuffles; was treated continuously until nine months of age with mercurial ointment.

Has not been treated since.

Child is apparently normal.

CASES MENTALLY BACKWARD.

No. 2, thirteen years, female.

History of Specific Infection. When a baby she had typical skin eruption and snuffles. Was treated at this time for a few weeks.

Subsequent History. Again at seven years, she had trouble with her eyes,—corneal ulcerations; also about the same time had swelling in both legs and arms. At present, her general health is good. She has old corneal scars, is wearing glasses, and has marked periostitis of the left tibia. Slight on the right. Mentally she is backward, being in the sixth grade only.

Prognostic Outcome. Unquestionably backward, but will not be dependent; probably will be able to support herself.

No. 6, twelve years, female.

History of Specific Infection. When a baby she had typical skin lesions and snuffles. Treatment lasted for a few weeks.

Subsequent History. When eight years old, she had sore eyes with corneal ulcerations; had breaking out on her neck and face and hair fell out. General glandular enlargements. Present condition: General health is apparently good; she still has general glandular enlargements; is wearing glasses; is only in the third grade, and is considered at school very inattentive and backward. The family history is: the mother has had five miscarriages, two deaths of premature infants. The oldest child, now 15 years old, has also had corneal ulcers, for which she is being treated at present. One child, five years old, has periostitis. One child died at nine years of age from what was termed "meningitis." There are six other living children who are apparently normal, according to the mother's statement, although they were not examined.

Prognostic Outcome. Physically good and mentally backward. Will probably not be dependent.

No. 9, four and one-half years, female.

History of Specific Infection. At three weeks of age developed typical skin erpution and snuffles; was treated for a few weeks with mercurial ointment.

Subsequent History. When three years old, she developed general twitching and staggering gait; was treated at that time again with mercurial ointment, and improved a good deal. Under treatment two months. At present the child can walk. No noticeable twitching; there have been no convulsions. She has had no corneal ulcerations, but is very near sighted. Mentally she is unquestionably backward.

Prognostic Outcome. Is poor as far as intellecual development goes. Physical development apparently will go on within normal limits.

No. 11, five years, male.

History of Specific Infection. First syphilitic symptoms appeared when 13 months old with hemiplegia and epileptiform attacks. He was treated at age of 13 months for four months continuously with mercurial ointment.

Subsequent History. Hemiplegia, and epileptiform attacks continued until he was four. Wassermann reaction at that time was positive and he was given 606. Since then he has improved markedly. His physical condition is apparently normal. He is mentally very backward. Father and mother in this case had both had active treatment. Father had beginning signs of tabes.

Prognostic Outcome for this child is that certainly of backwardness, if not some form of some more serious mental condition.

No. 12, sixteen years, male.

History of Specific Infection. When a few weeks old had snuffles and typical skin eruption. Was treated with mercury.

Subsequent History. He had apparently no return of the symptoms. Went to school and graduated from Grammar school when 16, and had just entered employment with an engraving company; at school he was considered dull; very inattentive and backward.

Prognostic Outcome. Mentality will certainly not improve. He, however, will not be dependent.

No. 13, nine years, male.

History of Specific Infection. When a baby had typical skin eruption and snuffles, for which he was treated with mercurial inunction for a few weeks.

Subsequent History. At age of seven began to have spells of being very apathetic with marked frontal headache and marked loss of memory. He had slight staggering gait. He returned to the hospital at this time, and was treated internally with mercury and K. I. Treatment was kept up for about two months, when he again disappeared, as he had apparently improved. At present he still has occasional headaches; he had no staggering; memory has improved markedly. Otherwise, his general physical condition is apparently good. In school he was very backward; was in the third grade, and it seems impossible for him to progress.

Prognostic Outcome is unfavorable; the probability is that mentally he will not develop any more, and is very likely, without treatment, to have more relapses, making him a dependent in time.

No. 14, ten years, male.

History of Specific Infection. When a few months old, had typical skin eruption and snuffles. Came to the hospital and was put on treatment, but did not follow it.

Subsequent History. At present he is in the school for feeble-minded. His general condition is very debilitated, and his mentality is that of an imbecile of a rather low grade. The family history in this case is indefinite, as there are no other children and the father deserted shortly after the birth of this child.

Prognostic Outcome. There can be nothing hoped for. The child will probably die early, as his physical condition, as well as his mental, is very poor.

No. 16, ten years, male.

History of Specific Infection. When two weeks old developed typical skin eruption and snuffles, with ulceration on face and body when seen at the hospital at two weeks of age. Treated with mercurial inunctions. Stayed on treatment only long enough for symptoms to disappear.

Subsequent History. Has not been treated since. Present condition is that the child is very small for his age, and has a very large, square head,—is very babyish in his actions and with the things with which he plays. Does not go to school because he cannot learn. Is markedly backward. Family history is that mother has had two children who died shortly after birth; there are three other children living, one of whom is very backward and has a very asymmetrical head; pupils are unequal. Mentality poor.

Prognostic Outcome. Is very poor; probably belongs to the imbecile group and should be in an institution.

No. 17, thirteen years, male.

History of Specific Infection. When a baby had typical skin eruption and snuffles. Was treated for a short time until these disappeared. At five and a half years of age again had recurrence of a slight eruption on cheeks; had swelling along the left leg, which was painful, and had numerous enlarged glands. At this time he was treated with mercurial ointment and K. I., with which he has been treated off and on ever since.

Subsequent History. At present his physical condition is fairly good. Mentally he is only in the third grade, very backward, inattentive. Probably will not be promoted this year. He has only gone to school about two years in his life.

Prognostic Outcome. Is very poor mentally. Probably will be a dependent, though he may be able to earn his living in some menial fashion.

No. 19, sixteen years, male.

History of Specific Infection. When a few months old, he had typical skin eruption and snuffles. He was treated with mercurial ointment over a period of a few weeks until these disappeared.

Subsequent History. At present he has typical saddleback nose; his general physical condition is fairly good; now at 16 years of age, he can hardly read or write. Is very inattentive and backward. Has hardly gone to school at all as he did not seem able to learn. He has a younger brother who has also been unable to learn anything at school, at nine years of age still being in the first grade.

Prognostic Outcome. Is very poor mentally. Undoubtedly belongs to imbecile group, and should have institutional treatment.

No. 21, thirteen years, male.

History of Specific Infection. When a few weeks old, he had snuffles and typical skin eruption; he was treated with mercurial ointment for only long enough for these to disappear.

Subsequent History. At six years of age there was a return of symptoms with ulcers on his leg and corneal ulcers, for which he was treated with mercurial ointment. For his eye trouble he is still being treated off and on as they recur. Also has taken K. I. most of the time. Present condition: his general health is fair. He has marked Hutchinsonian teeth and periostitis of both tibia and old corneal ulcers. Child is very inattentive at school, being only in the second grade, with very low standing; mentally very dull; is very nervous and inattentive.

Prognostic Outcome. Is poor mentally. Apparently a good subject for special training.

No. 24, seven years, male.

History of Specific Infection. When a few weeks old he had snuffles and typical skin eruption. Treated for a short time with mercurial ointment. Has not been treated since.

Subsequent History. Present condition: physically he is in good health. He has some speech difficulty and is very backward. Only in the first grade.

Prognostic Outcome,—that of a decidedly backward child,—probably will not be a dependent, though too early to say.

No. 36, four years, male.

History of Specific Infection. Symptoms appeared when two weeks old,—typical skin eruption and snuffles. Treatment consisted of mercurial ointment, which was continued for a very short time. Apparently has had no recurrence since.

Subsequent History. He has been apparently healthy physically. Is very nervous; has not been sent to Kindergarten. It is hard to judge his mentality,—apparently, below par. The father died of heart disease.

Prognostic Outcome. Some grade of mental backwardness. Probably not imbecile.

No. 37, three years, male.

History of Specific Infection. Symptoms typical skin eruption and snuffles when seven weeks old. Was treated with mercurial ointment and mercury internally. Treatment was continued over a very short period. Has not been followed up at all.

Subsequent History. Development of a nasal pharyngeal ulcer which perforated. He had no treatment for this. General condition, however, is fair. He cannot speak. Mentally it is hard to judge on account of his speech defect, but he seems considerably below normal. Father has beginning signs of tabes: mother has had one miscarriage, and five children died early or soon after birth. There are eight other children living; none are bright, but none apparently very abnormal from mother's description, although all the children not seen.

Prognostic Outcome. This child is certainly backward and may be some grade of imbecility.

No. 43, four and a half years, male.

History of Specific Infection. Typical symptoms of skin eruption and snuffles when a few weeks old. Treated internally with mercury over a period of a month. Has no treatment since.

Subsequent History. He was jaundiced until he was one and a half years of age and had a large liver. Did not begin to talk until he was three years of age. Didn't walk until he was one and a half years old. Present condition: physically is apparently normal; he does not talk very clearly yet, and mental condition is markedly backward.

Prognostic Outcome. Is probably that of some grade of imbecility.

No. 44, two years, male.

History of Specific Infection. Typical skin eruption and snuffles at two months of age. Was treated then with mercurial ointment for a few weeks. Has had no treatment since.

Subsequent History. He walked when a year and a half old. At present, when nearly three years old, can only say four or five words. Anterior fontanelle is still open; head is large; slightly hydrocephalic. He is both mentally and physically backward.

Prognostic Outcome. That of some grade of imbecility.

No. 48, two years, male.

History of Specific Infection. Had typical skin lesions and snuffles beginning when one week old. Was first treated when two and a half months of age with mercurial ointment for a very short time, returning to the hospital only twice.

Subsequent History. The general health now at two years of age is fairly good. In intelligence he appears below normal, but it is hard to judge. He is just beginning to walk; says only four or five words indistinctly. Has only 12 teeth.

Prognostic Outcome. He will probably be mentally backward—of what grade it is impossible at this time to say.

No. 52, two years, female.

History of Specific Infection. Typical skin lesions appeared during the first few weeks, and cleared up after a few weeks of treatment with mercurial ointment.

Subsequent History. She did not walk until one and a half years old. Now at two years old has only one tooth. Mentally does not seem at all bright. General health is fairly good.

Prognostic Outcome. She bids fair to be markedly backward mentally

No. 53, nine years, male.

History of Specific Infection. When two months old, had typical skin eruption and snuffles. He was treated with mercurial ointment at this time long enough for these to disappear.

Subsequent History. He is at present in fairly good physical condition. Has marked saddleback nose; periostitis of both tibia and keratitis. Reads with difficulty; only in second grade; speaks hesitatingly.

Prognostic Outcome. Certainly a backward mentality. Probably will not be entirely dependent.

CASES OF THOSE WHO DIED.

No. 1, died at six weeks of age, male.

History of Specific Infection. When two weeks old had snuffles and developed typical skin eruption; treated with mercurial ointment; child died when six weeks old suddenly, apparently from mother's description, of a sudden collapse. There is another child now 11 or 12 years old, who the mother says is bright, but does not get along well at school. Does not seem able to learn. Was not seen or examined.

No. 3, died at three years of age, male.

History of Specific Infection. When two weeks old developed typical snuffles and skin eruption, which was continued until these disappeared. When two and one-half years old, he had not walked at all. He was markedly mentally backward; at this time he developed periostitis; was put on a treatment at this time; child, however, failed rapidy, and died when three years of age. The family history: one child now 22 years old had eye trouble,—corneal ulcers when in school, and had to wear glasses and was backward, and did not finish even grammar school, before going to work. Second child who is now 18 years old is in the second grade of High School; she had typical specific lesions when a few weeks of age, and was treated; is now very delicate and has frequent headaches; she is under continuous treatment; mentally is backward, though not so poor but to be self-supporting.

No. 4, died when three and one-half months old, female.

History of Specific Infection. When a few weeks of age developed typical skin eruption and snuffles; treated with mercurial ointment without any improvement. The child died, apparently from malnutrition.

No. 5, died at six months of age, male.

History of Specific Infection. At the age of two months, developed skin eruption and snuffles, for which it was given mercurial ointment treatment, which continued for a month. General condition did not improve; steadily grew worse; apparently died in atrophic condition.

No. 8, died at seven weeks of age, male.

History of Specific Infection. At four weeks developed typical eruption and snuffles; treated with mercurial ointment. Child died when seven weeks old in convulsions. Mother has one other child now 10 weeks old who apparently has no signs as yet.

No. 20, died at seven weeks old, female.

History of Specific Infection. When a few weeks old she had typical snuffles and skin eruption. She was given mercurial ointment. Lesions, however, did not respond to treatment. She grew steadily worse, and died when seven weeks old from atrophy.

There are three other children in the family, one of whom is apparently normal; the other two show signs of specific infection.

No. 22, died when a year old, female.

History of Specific Infection. When two months old, developed typical snuffles and skin eruption. He was treated with mercurial ointment until these disappeared.

Child died suddenly—cause not given.

There are two other children in this family; oldest child nine years of age, who is only in the second grade at school and mentally dull. Second child six years of age also mentally backward.

No. 27, died at two years of age, male.

History of Specific Infection. When a few weeks old he had typical snuffles and skin eruption. Mother did not apply treatment. When one year and ten months old he developed jaundice which steadily increased; liver was very large; this continued until his death at two years of age.

No. 28, died at nine weeks old, male.

History of Specific Infection. When two weeks old, developed marked snuffles and typical eruption; treated with mercurial ointment. Apparently did fairly well until he developed some acute intestinal infection, which caused his death.

No. 31, died when two years of age, male.

History of Specific Infection. When two months old, developed typical eruption and snuffles; was treated with mercurial ointment; was kept on treatment only for a short time until skin eruption disappeared; was apparently fairly well until two years of age, when he developed what was called meningitis and died suddenly.

No. 34, died when seven months old, male.

History of Specific Infection. At three weeks of age, developed typical skin eruption and snuffles. Was treated with mercurial ointment. Condition did not improve under treatment, and he died when seven months old of apparently mal-nutrition.

No. 38, died at ten months, female.

History of Specific Infection. When three or four months old, she developed typical snuffles and skin eruption. She was treated with mercurial ointment until these disappeared. On treatment only a short time. She died when 10 months old of acute intestinal infection.

No. 39, died when thirteen months old, female.

History of Specific Infection. When three months old she had typical skin eruption and snuffles. She was treated with mercurial ointment until these disappeared. Child apparently did fairly well and died from convulsions when 13 months old.

No. 41, died at four and a half months old, female.

History of Specific Infection. When two weeks old, had marked skin eruption and snuffles; was treated with mercurial ointment. Child did not do at all well, gradually failed and died of mal-nutrition at four and one half months of age. Mother has only one other child, now six years old, who apparently is normal. From her history, her infection dates subsequent to the birth of this child.

No. 42, died when five months old, male.

History of Specific Infection. When one month old, had typical skin eruption and snuffles; was treated for a short time, with mercurial ointment.

Child died suddenly when five months old. Mother said of convulsions.

No. 46, died at two and one-half months old, male.

History of Specific Infection. Shortly after birth, developed marked snuffles and typical skin eruption; also had pseudo-paralysis, beginning in left arm when a month old. Treated with mercurial ointment, and improved somewhat.

Died of acute intestinal infection.

No. 47, died when 13 months old, male.

History of Specific Infection. When a few weeks old, had typical skin eruption and snuffles; treated internally with mercury.

Child died with acute intestinal infection when 13 months of age.

No. 49, died when seven months old, male.

History of Specific Infection. When two months old had typical skin eruption and snuffles. Treated with mercurial ointment for a long enough period for these to disappear,—a few weeks. Child developed pneumonia at seven months and died.

No. 54, died at 11 months of age, female.

History of Specific Infection. When two months of age had typical eruption and snuffles; was treated with mercurial ointment; child was kept on treatment long enough for these to disappear, and when about 11 months old child had convulsions and died. Mother gives typical history of specific trouble.

No. 61, died when one year old, female.

History of Specific Infection. When six weeks old had typical skin eruption and snuffles; was treated for a long enough time for these to disappear with mercurial ointment.

Subsequent History. Child failed slowly in general nutrition and died when about a year old. Mother since had another child, now 10 months old, who also has typical skin lesions, for which the child is being actively treated, and now at 10 months of age, child seems to be doing fairly well.

No. 63, died at six weeks of age, male.

History of Specific Infection. One or two weeks after birth had marked snuffles and typical skin eruption.

Subsequent History. Child developed cerebral symptoms at six weeks of age a few days after starting mercurial ointment treatment, and died in convulsions.

PROTOCOLS OF CASES OF CONGENITAL SYPHILIS.

19 CASES OF THE ONES APPARENTLY MENTALLY NORMAL.

NO.	AGE	SEX	SYMPTOMS	LENGTH OF TREATMENT	PRESENT CONDITION
7	3 years	Male	Snuffles and skin eruption.	Few weeks.	Physically and mentally apparently normal.
10	6½ years	Female	Snuffles, skin eruption, later headaches.	Few weeks.	Bright; normal.
18	11 years	Male	Snuffles, skin eruption. At 4, headaches, glandular enlargement.	Few weeks. Several months.	Physically normal; mentality medium.
23	7 years	Female	Snuffles, skin eruption.	Few weeks.	Physically normal, but nervous; mentally apparently normal.
25	6 years	Male	Snuffles, skin eruption; at 5 years, headaches.	Few weeks; at 5 years few weeks.	Physically normal; mentally normal.
26	15 years	Female	Snuffles, skin eruption; at 10, ulcers and keratitis.	Few weeks; at 10, short periods.	Physically normal; mentally normal.
29	4 years	Female	Snuffles, skin eruption.	2 months.	Physically and mentally normal for child of 4.
30	4 years	Female	Snuffles, skin eruption.	Few weeks.	Physically and mentally apparently normal.

32	4 years	Female	Snuffles, skin eruption.	Few weeks. Lately, off and on.	Below par physically; mentally apparently normal.
33	4 years	Female	Snuffles, skin eruption.	Off and on for 18 months.	Physically and mentally apparently normal for 4 years.
35	4 years	Male	Snuffles, skin eruption.	Few weeks.	Physically and mentally apparently normal for 4 years.
40	3 years	Female	Snuffles, skin eruption, condylomata.	Few weeks.	Physically and mentally apparently normal.
45	4 years	Male	Snuffles and skin eruption. Later sores generally.	Few weeks.	Physically and mentally apparently normal.
50	1½ years	Female	Snuffles and skin eruption.	Few weeks.	Physically slightly backward; mentally apparently normal.
51	14 months	Female	Snuffles and skin eruption.	Few weeks.	Normal for 14 months.
59	21 months	Female	Snuffles and skin eruption.	Few weeks.	Normal for 21 months.
62	5 years	Female	Snuffles and skin eruption.	Few weeks.	Apparently normal.
64	4 years	Female	Snuffles and skin eruption.	Few weeks.	Apparently normal for 4 years.
65	1½ years	Female	Snuffles and skin eruption.	8 months.	Apparently normal for 4 years.

19 CASES OF THE ONES MENTALLY BACKWARD.

NO.	AGE	SEX	SYMPTOMS	LENGTH OF TREATMENT	PRESENT CONDITION
2	13 years	Female	Snuffles, skin eruption, periostitis, keratitis.	Few weeks.	Backward; not dependent.
6	12 years	Female	Snuffles, skin eruption, keratitis, glandular enlargement.	Few weeks.	Backward; not dependent.
9	4½ years	Female	Snuffles, skin eruption, ataxia.	First few weeks. Later for 2 months.	Backward.
11	5 years	Male	Hemiplegia, and epileptiform attacks.	First for 4 months. Later at 4, "606."	Backward.
12	16 years	Male	Snuffles, skin eruption.	Few weeks.	Backward; not dependent.
13	9 years	Male	Snuffles, skin eruption. Later ataxia and cerebral symptoms.	First few weeks. Later, 2 months.	Backward; probably dependent.
14	10 years	Male	Snuffles, skin eruption.	Did not follow treatment.	Imbecile. Dependent.
16	10 years	Male	Snuffles, skin eruption.	Few weeks.	Imbecile. Dependent.
17	13 years	Male	Snuffles, skin eruption, periostitis, glandular enlargements.	First few weeks. Later, since 5½ years old, off and on.	Backward. Probably dependent.
19	16 years	Male	Snuffles, skin eruption.	Few weeks.	Imbecile. Dependent.
21	13 years	Male	Snuffles and skin eruption. At 6 years, keratitis and periostitis.	First few weeks. Since 6 years, off and on.	Backward; subject for special institution.
24	7 years	Male	Snuffles, skin eruption.	Few weeks.	Backward.
36	4 years	Male	Snuffles, skin eruption.	Few weeks.	Backward.
37	3 years	Male	Snuffles, skin eruption.	Few weeks.	Backward, probably imbecile.
43	4½ years	Male	Snuffles, skin eruption.	1 month.	Imbecile.
44	2 years	Male	Snuffles, skin eruption.	Few weeks.	Imbecile.
48	2 years	Male	Snuffles, skin eruption.	Few weeks.	Backward.
52	2 years	Female	Skin eruption.	Few weeks.	Backward.
53	9 years	Male	Snuffles, skin eruption, periostitis, keratitis.	Few weeks.	Backward.

21 CASES OF THE ONES WHO HAVE DIED.

NO.	DIED AT AGE OF	SEX	SYMPTOMS	LENGTH OF TREATMENT	PRESENT CONDITION
1	6 weeks	Male	Snuffles, skin eruption.	Few weeks.	Died suddenly.
3	3 years	Male	First, snuffles, skin eruption. At 2½, periostitis.	Few weeks. Treated till death.	Died.
4	3½ months	Female	Snuffles, skin eruption.	Few weeks.	Died from mal-nutrition.
5	6 months	Male	Snuffles, skin eruption.	1 month.	Died from mal-nutrition.
8	7 weeks	Male	Snuffles, skin eruption.	3 weeks.	Died in convulsions.
20	7 weeks	Female	Snuffles, skin eruption.	1 month.	Died from mal-nutrition.
22	1 year	Female	Snuffles, skin eruption.	Few weeks.	Died.
27	2 years	Male	Snuffles, skin eruption; at 20 months, jaundice.	Not followed.	Died, hypertrophic cirrhosis of liver.
28	9 weeks	Male	Snuffles, skin eruption.	Few weeks.	Died from acute intestinal infection.
31	2 years	Male	Snuffles, skin eruption.	Few weeks.	Died from meningeal trouble; whether specific not known.
34	7 months	Male	Snuffles, skin eruption.	Few weeks.	Died from mal-nutrition.
38	10 months	Female	Snuffles, skin eruption.	Few weeks.	Died in convulsions.
39	13 months	Female	Snuffles, skin eruption.	Few weeks.	Died of acute infectious diarrhea.
41	4½ months	Female	Snuffles, skin eruption.	Few weeks.	Died of mal-nutrition.
42	5 months	Male	Snuffles, skin eruption.	Few weeks.	Died suddenly.
46	2½ months	Male	Snuffles, skin eruption, pseudo-paralysis of arms.	Few weeks.	Died of acute intestinal infection.
47	13 months	Male	Snuffles, skin eruption.	Few weeks.	Died of acute intestinal infection.
49	7 months	Male	Snuffles, skin eruption.	Few weeks.	Died of pneumonia.
54	11 months	Female	Snuffles, skin eruption.	Few weeks.	Died of convulsions.
61	1 year	Female	Snuffles, skin eruption.	Few weeks.	Died of mal-nutrition.
63	6 weeks	Male	Snuffles, skin eruption.	Few weeks.	Died in convulsions.

THE RESULTS.

The results of this investigation show very clearly the need of a much further and more complete study into this condition, and it is with the hope of stimulating such studies that this brief and preliminary set of cases is put forward.

They bring out the following points, many of which need much further investigation, but all of which are very striking and have an important bearing in such a study:

1 The high early death rate. This may be due partly to the instructions not being followed out, but in great measure it must be admitted that this mortality might be lessened to a considerable degree if such cases could be very much more closely followed, insisting on maternal nursing and on continuance of specific treatment, the two cardinal points in the early management of such cases.

2 The high percentage of backward children. No attempt has been made to draw any absolute percentages in such a small number of cases, but it must be clear to every reader that something should be done when, out of sixteen children of school age suffering from any congenital disease, eleven are more or less mentally affected.

3 The lack of following up the initial treatment. As history after history shows, treatment was discontinued as soon as the eruption which, in most cases was what the mother had brought the child in for, had disappeared. The question here, of course, which might be raised is: Is the mother the one on whom the entire blame is to be put, or is this within the field of the medical service? This naturally raises a second

question,—whether the responsibility for completed treatment rests on the medical service? The writer feels that too often it is really the lack of a follow-up system being provided by the hospital, which would hold and keep hold of such cases, and see that they realize the inportance and understand the significance of the treatment.

4 This is, after all, a question of efficiency, and a question which must be, sooner or later, answered much more seriously than it is today in many hospitals.

Such results are certainly significant and deserve our closest attention from every point of consideration, and it is intended to follow these cases and as many more as possible over a considerably longer period, reporting on their progress from time to time.

CONTRIBUTIONS TO THE NEUROLOGY OF THE CHILD. III. FURTHER OBSERVATIONS UPON NERVOUS AND MENTAL SEQUELAE OF ENCEPHALITIS IN CHILDREN.

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AND

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THE outcome of a previous communication, dealing with convulsive tendencies during and after encephalitis, has given us added stimulus, not only to follow up a larger series of cases, but also to keep in touch with the living ones previously studied.* We drew attention at that time in our conclusions to the fact that many of the children (5) showed some motor or mental sequelae. We felt from this investigation that neither medicine in any narrow sense nor social service in any direction whatever could afford to neglect any condition which apparently leaves such a high percentage of nervous and mental symptoms in its train. We have tried to find out what changes have occurred in two years among the nine surviving cases which were examined in our first study, and have followed the subsequent history of later cases (17 in number), which have since been treated at the hospital or have been brought to our notice by more careful examination of older hospital records. We have tried to do this in such a way that our readers might be able to gain a better idea of the class of cases studied. For this reason we have outlined the history of each case. These descriptions are meant merely to illuminate the subsequent course, rather than the strictly hospital and immediate diagnostic or therapeutic aspects of encephalitis. We are at present interested in their subsequent medical and social development. We have accordingly in no case given a complete history, but have merely picked out points which would best picture each case to any one interested in following with us their subsequent medicosocial course, which resolves itself so often into a study of the mental outcome. Our charts follow the outline made in our first contribution.

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* The previous study first published in February, 1912, was made in 1910 and presented by one of us (E. E. S.) before the American Neurological Association meeting in Washington.

The protocols of all the cases, old and new, follow:—

SUBSEQUENT PROTOCOL OF OLD CASES.*

No.	Subsequent Course.	Present Condition.
1.	Steady improvement.	Internal strabismus.
2.	Died later.	No autopsy.
3.	Felt effects of illness 10½ years afterward both nervously and physically.	Perfectly normal boy.
4.	Effects of illness marked for two yrs. afterward.	Still drags right foot. Backward in school; much more nervous than before.
5.	It took 6 mos. to learn to walk short distance. Very forgetful—growing worse. Bad headaches twice a month.	Mentally deficient. Very nervous and excitable.
6.	Has not been able to control rectum since illness. Forgetful and nervous.	Asymmetry of face. Falls frequently and drops things. Mother thinks him behind other children.
7.	Went to Baldwinville soon after leaving hospital. Record of convulsions for last two years shows deterioration.	Epilepsy and mental deficiency.
8.	Epileptiform attacks began 7 months later. Has been admitted to Monson State Hospital (for epileptics).	Epilepsy and mental deficiency.

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* For complete protocol, see original article in BOSTON MEDICAL AND SURGICAL JOURNAL, Vol. clxviii, No. 9, p. 278.

No.	Subsequent Course.	Present Condition.
9.	Diag. poliomyelo encephalitis. Dragged one foot for a few days after going home.	Perfectly normal mentally and physically.
10.	Died.	No autopsy.
11.	Died.	Autopsy reported.
12.	Lost sight of.	
13.	Convulsions daily for 2 years. Since then attacks of crying daily (2 years). Has never walked or talked. 5 2-3 years old.	Spastic diplegic epilepsy. Mental deficiency.
14.	Died—no autopsy.	
15.	Uneventful.	Much more nervous than before illness.
16.	Has worn glasses for 1½ years. Strabismus has improved.	Internal strabismus.
17.	Talked in 2½ months after leaving hospital. Able to walk in three months.	Much more nervous than before illness. Speaks much more slowly. Arms are weak still. Twitches when angry.
18.	Uneventful.	Apparently normal child. School doctor says vision is defective.
19.	Uneventful.	Perfectly normal child.
20.	Since leaving hospital, 3 years ago has learned to walk, but falls frequently. Is 6 years old and says but a few words.	Feeble-minded. Epilepsy?

21.	Able to walk in 2 months after leaving hospital. Not able to run for 1½ years. Now runs awkwardly.	Gets tired easily—otherwise normal.
22.	Uneventful.	Perfectly normal boy.
23.	Uneventful.	Normal boy.
24.	Ever since leaving hospital has been nervous and irritable and gets tired easily.	Still nervous—gets tired easily.
25.	Died—no autopsy.	
26.	Died—autopsy U. 11-15.	
27.	Died—autopsy H. 11-672.	
28.	In 2 weeks could talk and could control rectum. Walked in 1 month. Twitched when excited for two months.	Very nervous. Difficult to manage in school. Candidate for a special class.
29.	Died—no autopsy.	

No.	Spinal Fluid.	Duration of Acute Attack.	Complications.	Condition when Discharged.
13.	30 cc. clear. No cells or organisms.	39 days	Otitis media.	Both ears discharging—Flaccid—much improved.
14.	Clear, not under pressure.	4 days	None.	Died—no autopsy.
15.	Clear, 5 cells per c.m.m.	8 days	None.	Perfectly well mentally and physically.
16.	1 c.c. no pressure—cell 40; 50 per c.m.m. More monos than polos.	9 days	Lobar pneumonia. Otitis media.	Mental condition about normal. Some difficulty in articulation.
17	Not done.	2 weeks	None.	Can count to 10 and say single words; unable to walk well; is still ataxic.
18.	25 c.c. cloudy, moderate pressure, 720 cells; mononuclears 96%. Glob. neg. No organisms.	9 days	None.	Walks well. P. E. negative. No sequelae noted.
19.	30 c.c. Clear under pressure, no clot; cells 120. No organisms. Poly's equal to mon's.	15 days	Double otitis media.	Very weak, but bright mentally.
20.	Clear, 20 cells per c.m.m. Half lympho's, half poly's.	21 days	None.	Nystagmus marked; internal strabismus; irritable and nervous. No rigidity.
21.	30 c.c. sl. increased pressure; 4000 cells (blood?). Lympo' only seen.	5 days	None.	Still uses right arm awkwardly; normal mentally. Sl. Kernig on left.

No.	Spinal Fluid.	Duration of Acute Attack.	Complications.	Condition when Discharged.
22.	Under pressure clear—480-3000 cells; no organisms; mono's 90%.	7 days	None.	Sl. weakness of right arm. Suggestion of neck sign.
23.	20-15 c.c. No pressure. Cell count 50; mono's 100%; glob. neg; no growth.	3 days	Pharyngitis. Tonsillitis.	Perfectly well mentally. Technical Kernig's on both sides.
24.	35 c.c. under pressure clear-cells 350—100% lymphocytes.	5 days	None.	General condition good. O.K. mentally.
25.	Clear, no clots; cells 120; noguelic glob. positive. Ross-Jones glob. positive; 80% monos.	14 days	Broncho-pneumonia.	Died—no autopsy.
26.	Few c.c. fluid under no pressure. Cells 65 per c.m.m.	24 hours	None.	Died. Diag., acute toxic encephalitis and septicemia. See autopsy.
27.	50 c.c. clear under pressure. No cell count. Neg. test positive (blog.).	4 days	None.	Died—see autopsy.
28.	2 c.c clear fluid obtained; cell count 10; no bacteria.	28 days	Peri-tonsillar abscess.	Unable to control bladder or rectum; could neither walk nor talk.
29.	20 c.c. clear fluid under high pressure; cell 10; 1 lymphocytes seen; no clot; no bact.; glob.	24 hours	None.	Died. No autopsy.

No.	Rigidity of Neck.	Cerebration.	Motor Involvements.	Reflexes.
13.	Yes.	Conscious but much prostrated.	Left arm in tetany. Opisthotonos.	K. J.'s present. Double Kernig, right Babinski.
14.	Not noted.	Moribund.	Complete right facial paralysis.	Not noted.
15.	No.	Conscious but very dull.	Ptosis of right lid.	K. J.'s obtained. No Kernig, Babinski, or clonus.
16.	No.	Delirium followed by apathy.	Ptosis of right lid. Difficulty in swallowing.	K. J.'s not obtained; sometimes slightly Kernig on left, sometimes suggestion of double Kernig.
17.	Yes.	Unconscious and "hysterical" alternately.	Spasticity and incoordination in voluntary movements.	K. J.'s exaggerated. No Kernig, no Babinski. Ankle clonus obtained but not sustained.
18.	Yes.	Conscious, irritable at first, fol. by lethargy.	Arms rather spastic. Incontinent and has difficulty in swallowing.	K. J.'s not obtained; no clonus, Babinski or Kernig.
19.	Yes.	Stupor.	None.	K. J.'s present. No Kernig. Babinski, or clonus.
20.	Slight.	Semi-comatose.	Slight ext. strabismus of right eye. Irregular twitchings.	K. J.'s active. Suggestion of neck sign. Kernig on left; no clonus; Babinski on right one.
21.	Yes.	Comatose.	Symmetrical twitching of both hands. Downward twitching of eye-ball.	K. J.'s lively; neck sign present, slightly Kernig on left, no clonus.

No.	Rigidity of Neck.	Cerebration.	Motor Involvements.	Reflexes.
22.	**Slight.**	Restless, irrational. and noisy.	None.	K. J.'s equal and lively. No Kernig, or clonus, or Babinski.
23.	Very slight.	Drowsy but answers questions.	None.	K. J.'s normal. Kernig on left. No clonus or Babinski.
24.	**Yes.**	Comatose.	Rigidity of arms and legs. Incontinence of urine.	K. J.'s not obtained. No clonus or Babinski.
25.	**No.**	Normal.	Strabismus and nystagmus. Twitching of right arm and leg.	K. J.'s on right. Absent on left. No neck sign, Kernig, Babinski, or clonus.
26.	**No.**	Semi-conscious. - Cyanotic.	Partial opisthotonos.	Right K. J. left. Double Babinski; no Kernig; no neck sign.
27.	**No.**	Normal until convulsions began.	Twitching of right of face and body. Right leg flaccid. No movement on left.	K. J.'s not obtained while in convulsion. Normal on entrance.
28.	**Yes.**	Slight delirious but conscious.	None.	K. J.'s not obtained. Babinski present. No Kernig.
29.	No.	Does not notice.	Convulsive movements of left side of face, arms and legs.	K. J.'s absent. No Kernig, clonus, or Babinski.

No.	Age.	Sex.	Temp.	Onset.	Convulsions.	Vomiting.	White Blood Count.
13.	11 mos. 23 days	F.	97-106	Acute	Yes	No	Not made
14.	2 wks. 3 days	M.	107	Acute	Yes	Yes	Not made
15.	6 yrs. 6 mos.	M.	104-98	Acute	No	Yes	12,200 8,800
16.	5 yrs. 11 mos. 14 days	M.	99-103	Acute	Twitching of mouth	Yes	16,800
17.	4 yrs. 2 mos. 26 days	F.	99-100	Acute	Yes	Not noted	11,800
18.	6 yrs. 5 mos. 7 days	F.	102-99	Acute	No	Yes	21,000 19,000 9,000
19.	3 yrs. 1 mo. 19 days	F.	99-105	Acute	No	Yes	14,400
20.	4 yrs. 7 days	M.	99-104	Gradual	Twitching	No	Not made
21.	2 yrs. 6 days	M.	99-103	Gradual	Twitching	No	12,100
22.	2 yrs. 9 mos. 15 days	M.	102-99	Acute	No	Yes	10,100
23.	7 yrs. 8 days	M.	98-101	Acute	No	Yes	22,000
24.	7 yrs. 2 mos	F.	99-101	Acute	Yes	Yes	1.000
25.	16 mos. 5 days	F.	101-104	Acute	Yes	Yes	40,000
26.	3 yrs. 3 mos. 8 days	M.	100	Acute	Yes	Not noted	Not made
27.	2 yrs. 3 mos.	F.	98-101	Acute	Yes	Yes	Not made
28.	7 yrs. 3 mos.	F.	98-101	Acute	No	Yes	26,000 42,000
29.	1 yr. 5 mos. 5 days	M.	105	Acute	Yes	Yes	Not made

RESULTS.

The facts elicited are surely striking, and are significant in the following ways:—

1. They illustrate the importance of what might be called sequence studies.

2. A further study has brought to light one more case of epilepsy, making 10% of our present total, a figure not inconsistent with general statistical expectation.

3. On the same general statistical grounds, we might have predicted that our number of mentally backward children would increase as the number investigated grew. In this group, we now have five children, two of whom are feeble-minded without any signs of epilepsy and three are cases of marked mental retardation or backwardness. (Not reaching the grade of feeble-mindedness—imbecility of English writers). This gives 28.5% of the living children who show marked mental defects.

4. There are four (or 15%) of these cases that show less marked residual effects from their encephalitis, (*a*) either by excessive "nervousness" or (*b*) because they show a much shorter reaction period to fatigue.

5. Two (or 7.1%) still show motor sequelae (strabismus).

6. 28.5% have died.

7. Only six (or 21.5%) of the children show no signs of their previous attack and are apparently normal in every way.

8. Tabulation of these results is as follows:—

Epilepsy Nos. 7, 8, 13, or 10.7%, or 7.1% not counting 13.

Feeble-minded, Nos. 5, 20, or 7.1%.

Backward, Nos. 6, 4, 28, or 10.7%.

Nervous or easily tired, Nos. 15, 17, 21, 24, or 14.6%.

Strabismus, Nos. 1, 16, or 7.1%.

Normal, Nos. 9, 3, 18, 19, 22, 23, or 21.5%.

Dead, Nos. 2, 10, 11, 14, 25, 26, 27, 29, or 28.5%, or 25% without No. 2.

28.5% show marked mental defect.

50% show some stigmata.

21.5% are normal.

28% died.

9. These results impel further investigation of these cases and of any other ones we may have occasion to follow from time to time. Our first endeavor has been to learn the dimensions of this problem (compare Lucas' work on sequelae of syphilis*) rather than to study any portion of it intensively. We now plan to make intensive studies on the cases we have so far followed and to individualize these more general conclusions.

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* Contributions to the Neurology of the Child. II. Note on the Mortality, and the Proportion of Backward Children, in a Series of Congenital Syphilis Followed Subsequent to Hospital Treatment; from the Out-Patient Department of the Children's Hospital and the Department of Pediatrics, Harvard Medical School, by William Palmer Lucas, M.D.

XXXIV

CLINICAL AND ANATOMICAL ANALYSIS OF ELEVEN CASES OF MENTAL DISEASE ARISING IN THE SECOND DECADE, WITH SPECIAL REFERENCE TO A CERTAIN TYPE OF CORTICAL HYPERPIGMENTATION IN MANIC-DEPRESSIVE INSANITY.

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AND

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(From the Laboratory of the Danvers State Hospital, Number 48 of Danvers State Hospital Series.)

This paper is the third in a series which attacks the Danvers State Hospital material by decades. It concerns itself with those cases which first showed mental symptoms in the second decade, and is intended for comparison with similar analyses of the fifth,[1] sixth and seventh[2] already published, and papers in preparation for the remaining decades.

The previous papers make an extended preface unnecessary. For our material we present abstracts of clinical histories followed by general autopsy findings, gross brain findings, and cursory notes of microscopical examination of the brain cortex with special reference to certain pigments best demonstrable by Heidenhain's iron-hematoxylin method.

Nine hundred and thirty-eight consecutive autopsies, in several of which age at onset was unknown, gave 18 cases with first attack between the ages of 11 and 20. In 5 of these brain material had not been saved and in 2 histories were lacking. Eleven cases were left for study—3 male and 8 female.

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[1] Southard and Bond: Clinical and Anatomical Analysis of Twenty-five Cases of Mental Disease Arising in the Fifth Decade. Am. J. Insan., 1914.

[2] Southard and Mitchell: Clinical and Anat. Analysis of Twenty-three Cases of Insanity Arising in the Sixth and Seventh Decades. Am. J. Insan., Oct., 1908.

Case Material.

Case 1 is that of a mulatto girl whose death followed the onset of her first mental illness in 20 days, at the age of 17.

Family history is negative. She lived on Island St. Kitts until 18 months before admission; since that time she worked hard at general housework. She had been strong and well and rather above the average in mental capacity.

Twelve days before admission she seemed to her family rather depressed and confused, but the family noticed nothing peculiar and she went back to her work for a few days. She fell fainting while at work and was sent home, where she moved about excitedly, laughed, sang, "rambled," gesticulated. Here she showed marked psychomotor activity, refused to eat food "because it was poisoned"; was good natured. She died suddenly on the eighth day.

Autopsy discovered an acute fibrinous exudate on pharynx, tonsils and tongue; acute otitis and leptomeningitis; acute congestion of lungs, liver and spleen; subcutaneous emphysema of cervical and mediastinal tissues; small aorta; brain weight 1340. (KL bacillus recovered from throat.)

Nissl, Pyronui and other stains showed "acute alteration" of the nerve cells, glial changes, infiltration by polynuclear cells, lymphocytes and a few plasma cells—all these changes most marked in the frontal region left.

There is little or no pigment in any region except the left superior frontal, where punctate small masses are found in moderate but singularly evenly distributed amounts. Almost every satellite and neuroglia cell has one or two small punctate masses, and some neuroglia cells in supragranular layers were noted, having a dozen or more granules, resembling the cells of cases much older (as examined in previous work). The question arises, whether the relatively severer acute and chronic inflammatory process which characterized this gyrus could have determined an alteration of cell metabolism such as we usually find in older cases.

Case 2 is a girl who died nine months after entering the hospital at 17.

Her father is insane (dementia præcox). The patient was born in Armenia and came to America when 5 years old. She was at work in the mills; in the evenings attended night and sewing schools.

Five days before entrance she expressed fears of the Catholics, of men, of negroes and devils and said that she had lived a lie for the last five years. In the hospital she at all times refused to answer questions, but would often talk and sing to herself—what she said seemed to have little connection if any. She was restless, her movements quick and tending to stereotypy; at the end of a month she had many mannerisms, was resistive, showed cerea flexibilitas and a little negativism. Her mood showed apparently neither depression nor elation. She was tube-fed. In six months tuberculosis developed, of which she died.

Autopsy showed merely an extensive tubercular process in the left lung. Brain weight, 1270.

This case is to be published more fully elsewhere with a description of microscopic findings; from the standpoint of this research, the Heidenhain staining pigments are absent or negligible in all areas so far studied.

Case 3 is that of a married woman whose first attack occurred at 17, second at 31, third at 32, and who came to this hospital at 49 to die six weeks later.

Father, mother and three brothers are living and well; an aunt is insane. A strong child, developing normally and doing well at school. At 17, in private (high) school she studied hard and became depressed, weak, kept quiet and had no active interest. At 31, and after an unhappy marriage at 32, she had similar attacks. In no attack did delusions appear. She made perfect recoveries. At 49 she came to this hospital in a typical manic attack which had lasted five months. She died of enterocolitis.

Autopsy showed unequal pupils, dilated stomach, chronic pleuritis and endocarditis, infarst of spleen, chronic hepatitis and sclerosis of the aorta, with acute pyelonephritis and enteritis.

The dura was thickened and adherent, the right ascending parietal artery enlarged and thrombosed. There was a softened hemorrhagic area 1 cm. in diameter, well defined, in right postcentral lobule, 2 cm. from superior surface. Brain weight, 1210.

Heidenhain preparations showed much pigment in the pyramidal cells everywhere, varying most in amount in the frontal region; much glial pigment in all regions except frontal, where it was moderate; much pigment in the perivascular spaces of calcarine and precentral regions, with little or none in temporal and frontal.

Case 4 is that of a single woman whose first mental trouble was at 19, who came to the hospital at 20 and at 22, dying at 25 after an interrupted residence.

An uncle had post-paralytic insanity; an uncle had epilepsy; grandmother paralytic; father alcoholic. "Patient had ordinary mental capacity to 19." She finished a common school course and worked in a factory for $7 a week.

She attempted suicide at 19 and at the Westboro State Hospital was found to be depressed and discharged recovered after several months. For several months at home she seemed well, then had a month's depression, after which she became very active and immoral. She was brought to this hospital, was at first only active and cheerful, but then went through a noisy, singing excitement, seeming almost well for a time, then growing depressed, then noisily excited, and then normal when she was discharged. An enlarged heart was noted on her entrance here. At home she got on well part of the time, but had spells of irritability and discouragement, and several times went off in the company of men. In a year she was returned to the hospital in a mild depression and after showing gradual improvement for a year was allowed to go out on visit. For a week she got on well and then resumed her immoral ways, being returned to the hospital two months later in a hyper-active condition, silly. Tuberculous infection of the lung soon appeared, and in a year she died; during this time she showed several attacks of excitement lasting for a day or two, and a few depressed spells.

Autopsy showed tuberculosis of the lungs with cavitation and bronchiectasis, tuberculosis of intestines, lymphnodes, miliary tubercles of liver and kidneys, amyloid reaction of spleen and liver, serous pericarditis and peritonitis, emaciation, decubitus, aortic sclerosis, chronic fibrous endo- and myocarditis, slight coronary sclerosis.

The brain weighed 1310 g. Dura slightly adherent, with pia slightly milky over parietal sulci. The frontal convolutions on the left are smaller and more numerous than on the right. Slight pial thickening over cord.

The microscope shows fewer cells in the small pyramid layer of left superior frontal gyrus than of right. The left occipital region seems poorer in cells in outer layers than the right. Superficial gliosis in many regions (see Neurochemical Series, 1906-7) and some satellitosis. Under Heidenhain a very slight pigmentation of nerve cells and glia without local variation.

Case 5 is that of a single woman whose first mental symptoms were noticed with the onset of convulsions at 13, who entered the hospital at 55 to die four years later.

There is a negative family history. The patient was well and bright as a girl; she was making good progress when her school work was interrupted by fits at 13. All that is known of her ensuing history is that the convulsions increased in number and severity along with a gradual dementia. Here she showed severe dementia-animal-like behavior and athetoid movements of the arms and hands. Ten days before her death the right hand was infected.

Autopsy showed a tuberculosis of the left apex, chronic interstitial nephritis, sclerosis of the aorta and coronaries, unequal pupils. Streptococci were grown from the incised wound of the hand.

The brain weight was 1010 g. The dura was adherent over small areas in each frontal region; it was of normal thickness.

A moderate amount of subpial edema. The right half of the brain appeared slightly larger than the left. To the touch the motor areas gave the most resistance. The cornua ammonis were smaller than usual; the ventricle walls finely sanded.

Microscopically the glial cells were very much increased, with marked satellitosis. Under the Heidenhain stain the pigment was large in amount and evenly distributed over glia, nerve cells and perivascular spaces.

Case 6.—A single woman, whose first mental symptoms appeared at 20, who entered the hospital at 23 and died six years later.

Family history negative. The patient was born in Newfoundland. She developed normally.

At 20 she began to be careless, at 22 had severe headaches with flushing of the face, and at 23, just before her entrance, she developed delusions about a man who she thought was following her. Here she was well oriented, showed considerable dulling of the finer sensibilities with loss of affect, possible auditory hallucinations, cheerful and nonchalant manner, refused to occupy herself. In a year many mannerisms appeared, in three years outbursts of violent excitement. After four years an epithelioma of the tongue was found; two years later she died with symptoms of pneumothorax. She was apathetic but never lost her orientation.

Autopsy showed emaciation, pulmonary tuberculosis, empyema, chronic pleuritis, chronic lymphnoditis, chronic peritonitis, myo- and endocarditis, acute and chronic nephritis, cystic tube (right), epithelioma of tongue and sub-lingual glands, cancerous growth of pituitary.

The brain weight was 1165 g. The dura was slightly thickened and adherent to the calvarium; the pia was thickened over the vertex. There was a large amount of subpial edema. The convolutions were symmetrical and firm.

With the Heidenhain stain pigment was found in extremely slight amounts in the glia and perivascular spaces of the right precentral lobe and was not found elsewhere.

Case 7 is that of an unmarried girl who came to this hospital in two attacks, one at 17 (or 14), the other at 31 (or 28), and who died three weeks after her last admission.

The paternal grandmother was insane, and the father and mother were both of very peculiar makeup. Home life was unhappy. A social, mild, capable girl. She worked in factories and in housework.

At 17 she felt very happy, restless, thought she was going to get married, was stage struck; throughout there seemed to be some indifference. This mood changed to a condition where she seemed depressed, indifferent, inactive. Both phases together lasted eight weeks. Her cervix and uterus appeared unusually large. She was well for 14 years. At 31, two months before admission, she became restless, laughed and talked incessantly at times, at other times cried, thought people were trying to injure her and that the food was poisoned. At the beginning of this attack her father and mother had separated. On second admission there was irregularity of heart action and a thrill was noticed over apex; tremor of arms and pectoral muscles. She talked dramatically, apparently uninfluenced by what went on about her; at times flight is noticed, but often the connection between sentences is not apparent. "I am a widow instead of an old maid. They poisoned all but my insides and they can never poison that." Whether she was oriented could not be determined. Hallucinations are probable. After tube feeding she died of lobar pneumonia.

Beside the pneumonia, right, the autopsy disclosed malnutrition, chronic atrophic dermatitis, chronic adhesions about gall bladder and appendix, right hydrosalpinx, chronic gastritis, acute colitis, dilatation of thoracic aorta.

The brain weight was 1300 g. The dura is not adherent. In a wedge shaped area including both first frontal convolutions, apex pointing back to the central fissure, there is considerable anemia in contrast to the rest of the brain. Section into the ventricles shows barely palpable granulations over the optic thalami.

"Microscopically the Nissl sections would serve to give an example of normal cortex. The right frontal region shows slight superficial glioses, and the white matter of both frontal regions shows excess of neuroglia nuclei. About a vessel in cerebellum is a cell collection suggesting chronic exudate. The cervical regions of the cord suggest posterior column gliosis."

In the precentral region there was considerable pigment in the nerve cells, a less and more variable amount in the glia and perivascular spaces. In the frontal region the pigment was very slight and in the calcarine areas negligible.

Case 8, a single woman, had a first attack of mental trouble at 15 or 16, received hospital treatment first at 20 to 23, was taken home and first brought to the Danvers State Hospital at 26, where she remained 19 years till her death.

Family history is negative. The patient was bright and was well educated. At 15 came a poorly described "attack which left her demented to some extent." At 20 apparently she was worse, and then for some years was "fairly reasonable." Then she began to have periods of depression and excitability, and several times attempted suicide. Menstruation was at times suppressed, at times painful. Brought here at 26; at first she seemed to enjoy it, then tried to escape and made a feeble attempt at suicide; became capricious, suddenly dropping her work or topic of conversation to switch off upon something else. Masturbation was noticed. At 30 she was boarded out for two months, being returned because of her restlessness. At 34 she was apathetic; at 41 her conversation loose and her voice unmodulated; at 43 tuberculosis was suspected; she showed negativism. Without much further change she remained to her death at 45.

The cause of death was pulmonary tuberculosis. The autopsy showed, in addition, emaciation, sclerosis of internal mammaries and aorta, hemorrhagic endocarditis, fatty liver, chronic cholecystitis, cholelithiasis, chronic parenchymatous nephritis, uterine fibroid, hemorrhage and ulceration of stomach and intestine.

The brain weight was 1385 g. The dura was not thickened and the pia showed only a slight clouding over vessels. The convolutions were well rounded and of normal consistency. The basal vessels were free of sclerosis.

The pigment was negligible, being found only in an occasional satellite cell.

Case 9 is that of a single man[3] whose first attack came at 12, who was admitted to this hospital at 19 and remained until his death at 32.

The paternal grandfather was intemperate. The patient possessed ordinary mental capacity and did well at school.

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[3] This case has been published as Case XIV by Southard in his study of dementia præcox, 1910.

At 12 he had a two weeks' attack of confusion and more or less unconsciousness. For some years after he would at times complain of a pain in his back or head. At 18 he was observed to have laughing spells, which would perhaps lead to boisterous outbreaks; he thought that someone was mesmerizing him. Then followed spells of elation and depression, insomnia, threats of violence and suicide. On admission he was quiet and expressed most fantastic and absurd scientific theories. "The moon is the blind eye of some animal." "I have the shoulders of an Egyptian, the head of Napoleon or an Italian and my limbs are French." "We are all being continually acted upon by minerals . . . . and magnetism."

The pigment under Heidenhain was negligible.

Case 10 is that of a single man whose age at the onset of the first mental symptoms was 17, and who came to this hospital at 19 and at 22, dying 7 weeks after his second admission.

Family history seems good. The patient was born in Canada, learned to read but not to write, was a good boy, made no trouble, had to go to work in the mill at 12. He worked steadily for five years.

At 17 he gave up work, and lay about the house smoking excessively. At 18 he had weak spells, which were explained by a doctor as due to tobacco heart. Until a month before entrance he was extremely dull, sleepy and inactive; since that time he has been excitable, violent, claiming that his mother was the devil. Admitted at 19, he showed a striking reaction to physical examination, twisting, turning, and suddenly allowing himself to be lifted as a dead weight, or stiffening and falling. No relevant answers could be obtained; there was much apparently disjointed production. For the next 14 months he was generally mute and resistive, but occasionally obeyed commands in an automatic manner. Transferred to another hospital, he was taken home after a month, where for a year he sat about and did nothing, during the next year having spells of a mild, peculiar excitement. Again committed to this hospital, at 22, his most prominent symptoms were untidiness and apathy; after seven weeks he died of dysentery.

Autopsy showed irregular pupils, apical scar, a limited aspiration pneumonia, injection of the mucosa of the gastro-intestinal tract with areas of denudation, acute nephritis, contracted bladder, enlarged mesenteric lymph-nodes, perforated drums in middle ears.

The brain weighed 1335 g. Somewhat soft at occipital pols. Slight pigmentation of cerebrum; none of cerebellum. Pia and dura were thickened.

Microscopical examination showed a considerable round cell infiltration. Everywhere there occurred a very slight but fairly regular nerve-cell pigmentation, with only occasional traces of pigment in glia or perivascular spaces.

Case 11 is that of a married man whose mental illness began at 18 or 20 and who came to this hospital at 58. After seven more admissions he died here at the age of 68.

Family history is negative. He was a cheerful, temperate man. There was a history of frequent attacks of depression from the age of 18 or 20. At 58 he was admitted in a depression from which he recovered in three weeks. At 59 he stayed five weeks in another depression, recovery being coincident with a follicular tonsilitis. In the same year came another depression of two months; at this admission his heart was noticed to be enlarged. At 60 a depression lasted three months. At 62 he was manic one month, depressed one week, and then became normal. At 65 he returned incoherent and euphoric for four days, and then for three years to his death depressed, confused and elated episodes followed each other.

At autopsy was found contracted kidneps, cardiac hypertrophy and dilatation with general edema. The coronary arteries were atheromatous. Lobar pneumonia and a hemorrhagic infarct of the lung were found.

The dura was adherent and the basal arteries moderately atheromatous. Brain weight, 1290.

Under the Heidenhain stain there was much pigment in the nerve cells, less in the glia and least in the perivascular cells.

Clinical Summary.

SEX.

We are dealing with a group of eight women and three men.

HEREDITARY FACTORS.

In six cases insanity in the family is denied; in five cases it appears; in three cases it is prominent; in Case 7 the father and mother were peculiar and the paternal grandmother insane; in Case 4 the father was alcoholic, an uncle epileptic, an uncle insane, a grandmother paralytic; in Case 2 the father was insane. In Case 3 an aunt was insane and in Case 9 the paternal grandfather alcoholic.

Antecedent Factors.

No antecedent factors appear which can reasonably be considered causal. The first three cases worked hard, and cases 3 and 7 had unhappy home lives.

Hallucinations of any sort are doubtful; auditory ones are probably present in cases 7 and 6.

One case (3) showed no delusions; in another case (10) they were doubtfully expressed. The only case showing either delusions of influence or of somatic character was 9. Delusions of persecution characterized 4 cases (1, 2, 6, 7).

GENERAL CLINICAL FEATURES.

Case 1 showed confusion. Six cases (1, 3, 4, 7, 8, 11) at times showed depression, and five (1, 3, 4, 7, 11) at times showed exhilaration. Four showed apathy (6, 7, 8, 10). Four showed excitements (4, 6, 8, 10); negativism appeared in cases 2 and 6. Case 5 had convulsions and athetosis. Cases 9 and 10 were catatonic.

Headache and vaso-motor disturbances characterized onset in Case 6. Menstrual disorders were noted in two women (7, 8), loose sexual habits in one (4), and self-abuse in another (8). Extreme weakness at onset is noted in one case (3). Cancer developed in one case (6); heart disease in cases 4, 7, 11; body pain in Case 9.

The general courses of the cases, and probable diagnoses, are summarized in the following table.

TABLE I.

Case.	Sex.	Age at			Duration of		Diagnoses.
		Onset.	Subsequent Attacks.	Death.	Attacks.	Life.	
1	F.	17	—	17	20 d.	20 d.	Manic-depressive psychosis?
2	F.	17	—	17	9 m.	9 m.	Dementia præcox.
3	F.	17	31, 32	49	2 y.?	32 y.	Manic-depressive.
4	F.	19	Many attacks.	25	3 y.?	6 y.	Manic-depressive.
5	F.	13	Gradual dementia.	59	Many y.	46 y.	Epileptic dementia.
6	F.	20	—	29	9 y.	9 y.	Dementia præcox.
7	F.	17	31	31	5 m.	14 y.	Manic-depressive.
8	F.	15	Many exacerbations.	45	30 y.	30 y.	Dementia præcox.
9	M.	12	18	32	15 y.?	20 y.	Dementia præcox.
10	M.	17	—	22	5 y.	5 y.	Dementia præcox.
11	M.	18	Many attacks.	68	20 y.?	50 y.	Manic-depressive.

ANATOMICAL ANALYSIS.

Six of these cases showed severe tubercular lesions (4, 5, 6, 8, 9, 2) and five were emaciated at death (4, 6, 7, 8, 9). Atheroma was found in five instances; coronary alone in case 11; aorta alone in case 3; aorta and coronary in cases 5 and 4 (age 25); aorta and internal mammaries in case 8. Cardiac hypertrophy was found in case 11; endocarditis acute in 8 and chronic in 6, 4 and 3; myocarditis in 6 and 4. Acute nephritis in 3, 6, 9, 10; chronic in 4, 6, 8, 11. Lesions of the gastro-intestinal tract are recorded in six instances; of the liver in two; of spleen in one; chronic peritonitis in three. Skin lesions appeared in cases 9 and 7. The first case had acute otitis media and the tenth perpration of the drum. A uterine fibroid was found in case 8, and hydrosalpinx in cases 6 and 7. Diphtheria was the cause of death in case 1, and pneumonia in case 11, pyothorax appeared in case 6 and hydrothorax in 9. The first case had a small aorta.

Brain weights with age at death are arranged in the following table:

TABLE II.

Brain Wt.	Age at Death.	Sex.	Case Number.
1010	59	F.	5
1110	32	M.	9
1165	29	F.	6
1210	49	F.	3
1270	17	F.	2
1290	68	M.	11
1300	31	F.	7
1310	25	F.	4
1335	22	M.	10
1340	17	F.	1
1385	45	F.	8

Inflammation of the meninges we find in nine cases; of the dura in cases 3, 4, 6, 10, 11; of the pia in cases 1, 4, 5, 6, 8, 9, 10. In case 3 there was a chronic inflammatory exudate near the vessels of the frontal region. The only instance of basal atheroma occurred in case 11, 68 years old. Cases 5 and 7 showed granular ependymitis locally. Precentral gliosis was noted in case 5, and postcentral softening in case 3; increase of pigment (gross) in 10; local anemia in 7; variation in convolutions of the two sides in 4 and 5; enlargement and thrombosis of the right ascending parietal artery in case 3, aged 49.

The cord in case 10 was small, to correspond with the small brain.

The distribution and amount of pigment was shown in the two following tables, the first arranged according to duration of life after onset, and the second according to the age at death. We have represented no pigment by o, slight by +, moderate by ++, marked by +++, and an extreme amount by ++++.

TABLE III.

Pigment Distribution and Duration of Life after Onset.

Case.	Duration Life After Onset.	Perivascular Cells.	Glia Cells.	Nerve Cells.
11	50 y.	+	+ +	+ + +
5	46 y.	+ + +	+ + +	+ + +
3	32 y.	+ + +	+ + +	+ + +
8	30 y.	o	o	o
9	20 y.	o	o	o
7	14 y.	o to + +	o to +	o to + +
6	9 y.	o	o	o
4	6 y.	+	+	+
10	5 y.	o to +	o to +	+
2	9 m.	o	o	o
1	20 d.	o	o	o

Case 1. More pigment in left superior frontal. Inflammation.

Case 3. Frontal pigment least.

Case 6. Precentral has slight pigment in glia and perivascular spaces.

Case 7. Precentral has moderate but variable pigment in pyramids and perivascular spaces.

TABLE IV.

Pigment Distribution and Age at Death.

Case.	Age at Death.	Perivascular Cells.	Glia Cells.	Nerve Cells.
11	68	+	+ +	+ + +
5	59	+ + +	+ + +	+ + +
3	49	+ + +	+ + +	+ + +
8	45	o	o	o
9	32	o	o	o
7	31	o to + +	o to +	o to + +
6	29	o	o	o
4	25	+	+	+
10	22	o to +	o to +	+
2	17	o	o	o
1	17	o	o	o

Conclusions.

1. This work is another instalment of work designed to throw light on the age-factor in the production of mental disease, and has the same features of random selection, employing only autopsied

cases, from a long series, as did previous work from the Danvers State Hospital laboratory on cases having onset in the sixth and seventh decades (1908) and in the fifth decade (1913).

2. There turned out to be surprisingly few cases for the analysis; somewhat less than 2 per cent of a long series of autopsied cases (18 in 938) proved to be cases having onset of mental disease between 10 and 20 years.

3. The age-distribution in the 11 cases which proved suitable for full clinical and anatomical correlations is striking; of these 11, 8 had onset between 17 and 20 years, and 5 (of these 8) at 17; the age-distribution, so far as it goes, suggests disorder at puberty as somehow related with the onset of the first attack.

4. Omitting one female epileptic which demented, we find the cases equally distributed between manic-depressive insanity and dementia præcox. The manic-depressive five were composed of 4 females (1 of rather doubtful diagnosis) and 1 male. The dementia præcox five were composed of 3 females and 2 males. Four of the five dementia præcox cases were subject to tuberculosis; one of the manic-depressives was tuberculous.

5. The lipoid disorder, of which we attempted to get an index by a study of the distribution of certain substances stainable by the Heidenhain iron-hematoxylin method, was far more in evidence in the manic-depressive series than in the dementia pr&cox series.

6. The three cases with most marked pigmentation (in this specialized sense) were: (a) the epileptic dement above mentioned, onset at 13, attacks till death at 59; (b) a manic-depressive, depressed at 17, 31 and 32, maniacal at 49, dead of intercurrent disease at 49; and (c) a manic-depressive, very numerous attacks of depression, first at 18-20, 7 known attacks between 58 and death at 68. Other three manic-depressive cases showed marked (although less marked) pigmentation focally in (d) the doubtful case above mentioned (in which indeed the pigment is rather an index of local metabolic disorder in an inflamed convolution) and (e, f) cases dying at 25 and 31 respectively.

7. The dementia præcox cases either showed no pigment as in (g) death at 17 after 9 months symptoms, (h) death at 45 after 30 years of symptoms, (i) death at 32, 20 years after onset, or a slight amount, as in (j) death at 29 after 9 years of symptoms,

and (k) death at 22 after 5 years of symptoms (pigment in occasional pyramids).

8. If these findings should be taken at their face value, it might be inferred that manic-depressive insanity is more likely to prove a disease involving brain-cell metabolism than is dementia præcox. In dementia præcox there is more evidence that certain cells have been destroyed outright; but cells which escape destruction are not likely to look in any respect abnormal. In manic-depressive insanity there is not such good evidence of cell-destruction; on the other hand, these cases seem to show that overloading with a certain kind of pigment is more characteristic of the brain-cells of manic-depressives than of precocious dements.

9. The manic-depressive cases of this series seem to have shown more depression than mania; what the relation of this may be to the histology of these cases is doubtful; but it would seem desirable to examine cases of long-continued mania and long-continued depression with the same technique.

10. Previous work from this laboratory on age-correlations with pigment-deposits has suggested that especially the neuroglia cells are likely to show progressively more and more pigment with advancing age; the present work, regardless of the special entity correlations just discussed, seems to show that youthful cases do not show much neuroglia-cell pigment, and therefore this work is to that extent consistent with former results.

11. As to the possible causes of the pigment deposits in various types of cell, perhaps nothing better than the mystic term "metabolic" can be risked. Still, there are two cases in which they were decidedly local accumulations of somewhat similar-looking substances due to or closely associated with acute inflammatory processes (see cases 1 and 10, dying at 17 and 22 years respectively). In these cases, to a large extent entirely free from pigmentation, either the pressure or the toxines of the inflammation had producd the same appearances *focally* that are shown by other non-inflammatory cases *diffusely*. The deposits are, then, possibly favored by certain factors working *ab extra* with respect to the cells in question.